Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy

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ABSTRACT

Background: Early recognition and accurate risk stratification are important in the management of arrhythmogenic right ventricular cardiomyopathy (ARVC). Identification of predictors of outcome by cardiovascular magnetic resonance (CMR) in patients undergoing evaluation for ARVC is limited. We investigated the predictive value of morphological abnormalities detected by CMR for major clinical events in patients with suspected ARVC.

Methods: We performed a longitudinal study on 369 consecutive patients with at least one criterion for ARVC. Abnormal CMR was defined by the presence of one of the following: increased right ventricular (RV) volumes, reduced RV ejection fraction, RV regional wall motion abnormalities, myocardial fatty infiltration, and myocardial fibrosis. The end-point was a composite of cardiac death, sustained ventricular tachycardia, ventricular fibrillation, and appropriate ICD discharge.

Results: Twenty patients met the composite end-point over a mean follow-up of 4.3 ± 1.5 years. An abnormal CMR was an independent predictor of outcomes (p < 0.001). The presence of multiple abnormalities heralded a particular high risk of events (HR 23.0, 95% CI 5.7–93.2, p < 0.001 for 2 abnormalities; HR 35.8, 95% CI 9.7–132.6, p < 0.001 for 3 or more abnormalities). The positive predictive value of an abnormal CMR study was 21.0% for an adverse event, whilst the negative predictive value of a normal CMR study was 98.8% over the follow-up period.

Conclusions: CMR provides important prognostic information in patients under evaluation for ARVC. A normal study portends a good prognosis. Conversely, the presence of multiple abnormalities identifies a high risk group of patients who may benefit from ICD implantation.

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1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterised by fibro-fatty replacement of the myocardium and a tendency for ventricular arrhythmias and right ventricular failure. ARVC has an estimated prevalence of 1 in 2000 to 5000 which frequently presents with palpitations and syncope, and is a leading cause of sudden cardiac death (SCD) in the young [1]. Diagnostic consensus criteria were originally defined in 1994 and based on a combination of morphological, histological, electrical, and clinical parameters which were weighted into minor and major criteria according to their relative significance [2]. Since then, much of the understanding of this entity has been driven by advances in genetics and imaging, and the ensuing progress has been incorporated in modified criteria which have been recently published [3]. Despite recent advances, the diagnosis of ARVC remains challenging, especially at the early stages of the disease, where patients may be left unrecognized and at an increased risk of SCD [4]. Reports suggest that early identification translates into significant improvements in survival [5]. Appropriate screening is hence pivotal for the management of patients with ARVC.

Cardiovascular magnetic resonance (CMR) is currently one of the main imaging modalities for assessing patients with suspected or known ARVC, as a result of a superior depiction of the RV and the ability of non-invasive myocardial tissue characterization. This has been supported by several publications showing a high diagnostic accuracy.
for ARVC [6,7]. However, there is little evidence on imaging predictors of outcomes in patients in whom a diagnosis of ARVC is suspected. We therefore sought to evaluate the prognostic value of CMR in a population referred to assess the presence of ARVC.

2. Methods

2.1. Study population

This was a longitudinal cohort study with prospective patient identification and CMR analysis, and retrospective event data collection. Consecutive patients with suspected ARVC referred for a CMR scan were recruited between 2002 and 2005 from a network of centres in southeast England. Inclusion was determined by the presence of at least one diagnostic criterion (minor or major) for ARVC according to the 1994 Task Force diagnostic guidelines [1]. All patients consented to this study which was approved by the local ethics committee.

2.2. Cardiovascular magnetic resonance

CMR was performed on a 1.5 T Siemens Sonata or Avanto (Siemens, Erlangen, Germany) using a previously described standardized imaging protocol for the right ventricle (RV) [7]. Steady-state free precession breath-hold cine were acquired in the long-axis planes for both the left ventricle (LV) and RV, including the RV outflow tract view. Sequential 7 mm short axis slices (3 mm gap) from the atrio-ventricular ring to the apex were also acquired, as were sequential transverse slices from the level of the pulmonary valve to the base of the heart. T1-weighted turbo spin echo images (field of view 300 mm, field of view phase ≥ 75%; TE 4.9 ms, pixel size 1.2 × 1.2 mm, 6–7 mm slice thickness with 3–4 mm gap) were also acquired as sequential transverse slices from the level of the pulmonary valve to the base of the heart. Reflecting a change in protocol and the evidence base, all patients scanned after 2003 received gadolinium contrast agent. Late gadolinium enhancement (LGE) images (field of view 300–400 mm, field of view phase 60–75%; flip angle 20°, pixel size 1.6 × 1.6 mm, 8 mm slice thickness with 2 mm gap, inversion time 320–440 ms) were acquired at least 5 min after intra-venous gadolinium-DTPA injection (Schering, Berlin, Germany; 0.1 mmol/kg) in identical long-axis and short-axis planes using an inversion-recovery gradient echo sequence [8]. Inversion times were adjusted to null the normal left ventricular (LV) myocardium, and imaging was repeated for each slice position in 2 separate phase-encoding directions to exclude artefacts.

2.3. Image analysis

Ventricular volumes and ejection fraction were assessed from the serial short axis cines using semi-automated analysis software (CMR Tools, Cardiovascular Imaging Solutions, London, UK) which permits correction for valve motion. The values obtained were indexed for body surface area (BSA), and adjusted for age and sex according to previously published reference ranges using the same methodology [9,10]. Volumes and ejection fraction were considered abnormal if they fell outside the normal reference range for age and gender. Regional wall motion abnormalities (RWMA) of the RV were subjectively assessed by an experienced observer. Localized aneurysms were defined as akinetic regions of the right ventricular wall showing bulging in diastole and systole. Fat infiltration was defined as the presence of high signal on T1 weighted images in any area within the myocardium. LGE was deemed present if an area of signal enhancement could be seen in short-axis views in two different phase-encoding directions and in a corresponding long-axis view (Fig. 2).

The CMR analysis was performed by an experienced observer (DJP, RHM, PJK, SKP) at the time of the study. All scans were reported prospectively, and therefore the observers had no access to outcome data. A CMR scan was considered abnormal if one of the five typical features of ARVC was present: increased indexed RV end-diastolic volume (RVEDV), decreased RV ejection fraction (RVEF), RV regional wall motion abnormalities (RWMA), fatty infiltration on T1-weighted spin-echo images, and LGE. Further analysis was performed by an experienced observer (FA) in 30 random patients to assess inter-observer variability. Patient information was removed from the images before viewing to ensure blinding.

2.4. Follow-up

The CMR findings were integrated with the remaining work-up for ARVC, and diagnosis of this condition was based on the recently revised ARVC Task Force criteria [3]. Conversely, patients with an alternative diagnosis to ARVC after initial work-up were excluded from the follow-up analysis (Fig. 1). Information regarding the work-up for ARVC and subsequent follow-up was obtained from a standardized patient questionnaire, and from clinical letters provided by the referring physicians and general practitioners. All patients were followed-up by their general practitioners. Medical records were reviewed after attendance at every outpatient clinic or after each hospitalization. Information about the cause of death was obtained from the National Office of Statistics and the National Death Registry. The end-point was a composite of cardiac death, sustained ventricular tachycardia, ventricular fibrillation, and appropriate ICD discharge. Sustained ventricular tachycardia and ventricular fibrillation were defined as per current guidelines on ventricular arrhythmias [11]. ICDs were implanted at the discretion of the attending physician. ICD discharge for the parameters programmed was deemed appropriate after review by an electrophysiologist.

2.5. Statistical analysis

Normally distributed continuous data are presented as mean ± SD, whilst categorical variables are presented as percentages. The baseline characteristics of the two groups (normal vs. abnormal CMR scans) were compared with the independent sample t-test for continuous variables, and chi-square test for categorical variables. A Cox proportional hazards model was used to test the association of variables with the composite endpoint. As there were only 20 outcome events, it was not feasible to carry out an unrestricted multivariate analysis. Instead, any clinical variables which were found to be significant on univariate analysis were individually tested alongside the CMR abnormality variable. Cumulative event rates were compared by the Kaplan–Meier method using the time to first event. The log-rank test was used to compare the Kaplan–Meier survival curves. A two-sided p value of <0.05 was deemed significant. All statistical analyses were performed using Stata 12.1 (StataCorp, Texas).

3. Results

3.1. Patients

Three-hundred and sixty nine consecutive patients were originally enrolled in this study. The indications for the CMR study are presented in Table 1. Fourteen of these 369 patients had their studies repeated because of suboptimal image quality due to frequent ectopic beats. Despite the use of oral antiarrhythmics in the repeat studies, the image quality was still not diagnostic in 3 patients who ultimately were excluded from the final analysis. Forty-three patients were further excluded after the initial diagnostic evaluation established an alternative diagnosis to ARVC. The baseline characteristics of the final 323 patients representing the outcome population (50% male, mean age 42 ± 16 years) are summarized in Table 2. Transthoracic echocardiography

![Fig. 1. Study flow-chart. ARVC = arrhythmogenic right ventricular cardiomyopathy; LV = left ventricle; RV = right ventricle; RWMA = regional wall motion abnormalities; VT = ventricular tachycardia.](image-url)
was performed in 268 patients (the other 55 patients underwent direct CMR as their primary imaging investigation). Electrophysiological studies (EPS) using a standard Wellens protocol were performed in 36 patients, of whom 23 had VT induced by programmed ventricular stimulation.

### 3.2. CMR

Cine imaging to calculate ventricular volumes and ejection fraction and to assess regional wall motion abnormalities was performed in all but the 3 patients with non-diagnostic image quality for volume analysis. T1-weighted spin-echo imaging was attempted in all patients, but image quality was deemed non-diagnostic in 21 patients (poor image quality due to arrhythmia). Contrast imaging with gadolinium was intended in 240 patients, but was not performed or analyzed in 3 patients (poor image quality, adverse reaction to contrast, and pregnancy). There was no significant statistical difference in baseline characteristics between those who underwent contrast imaging and those who did not receive contrast.

Eighty-one patients (25.1%) had an abnormal CMR scan. Patients with abnormal CMR scans were older, were more often males, had more frequent history of ventricular tachycardia and cardiac arrest, abnormal RV on echocardiogram, and were more frequently medicated with beta-blockers and amiodarone than those with normal baseline CMR scans (Table 2). Within the group of 81 patients with abnormal scans, 36 (44%) patients had increased RVEDVi, 37 (46%) had decreased RVEF, 50 (62%) patients had RWMA of the RV, 18 (25%) had fatty infiltration (involving the LV in 3 patients and the RV in 15 patients).
RV in 17 patients), and 15 (28%) had LGE (involving the LV in 12 patients and the RV in 7 patients). All 5 individual CMR variables correlated strongly with each other (p < 0.001). Interobserver variability of RVEDVI and RVEF was comparable to previous studies [12,13]. Agreement between categorical variables was generally good, with significant kappa agreement for RWMA and LGE imaging, but only fair kappa agreement for fat on T1 imaging (Table 3).

### 3.3. Follow-up

Based on an evaluation of the complete clinical data including all test results, a final diagnosis of ARVC according to the revised diagnostic criteria was made in 28 patients, whilst 12 patients had borderline diagnostic criteria and 15 patients met possible diagnostic criteria for ARVC (Fig. 1). Twenty-six additional patients had isolated abnormalities of the RV (10 with RV dilatation, 7 with isolated RV fat infiltration, 6 with regional wall motion abnormalities, 2 with isolated RV dysfunction, and 1 with isolated LGE in the RV), but not meeting criteria for ARVC according to the recent consensus document [3].

During a mean follow-up period of 51.5 ± 17.8 months, there were 7 deaths, 3 of which were cardiac in origin. Two patients died of right heart failure, whilst the remaining patient died due to ventricular tachycardia. All 3 patients had definitive clinical criteria for ARVC. The latter patient had the diagnosis of ARVC confirmed by post-mortem examination (Fig. 3). Six patients experienced sustained VT: 4 patients had VT as the cause of hospital admission, 1 developed VT during admission, and the other one had VT detected by ambulatory monitoring. All episodes of VT were associated with heart rates > 180 per minute, and were terminated by electrical cardioversion (except for the VT detected by ambulatory monitoring which terminated spontaneously). An ICD was implanted in 41 patients, of which 11 received appropriate shocks. The composite end-point of cardiac death, sustained ventricular tachycardia, ventricular fibrillation and appropriate ICD discharge was therefore met by 20 patients. Of these 20 patients, 17 had an abnormal CMR at baseline. Conversely, of the 242 patients with a normal CMR at baseline, only 3 had a serious event.

Of the 20 patients who met the composite end-point, 7 had a diagnosis of definite ARVC, 4 had a diagnosis of borderline ARVC, and 3 had a diagnosis of possible ARVC at baseline. The other 6 patients remained with 1 minor criterion for ARVC after CMR evaluation (1 with isolated RV dilatation, 1 with isolated RV dysfunction, 1 with isolated LGE in the RV, and the other 3 with normal studies). The 3 patients with a normal CMR study who met the composite end-point are detailed further: 1) A 61-year-old male referred with non-sustained VT of LBBB morphology, who had LBBB VT one year later during a hospital admission due to bronchopneumonia, which was the cause of his death; 2) A 69-year-old female referred post cardiac arrest with a dilated right ventricle on echocardiogram. RV size and function were normal by CMR. An ICD was implanted and she had an appropriate discharge 50 days later for VF. No discharges since; 3) A 57-year-old male referred with non-sustained VT of LBBB morphology on Holter. He was admitted one year later with RVOT ectopy and VT. Interestingly a follow-up CMR study detected new mid-wall fibrosis in the inferior wall that was not present on the index scan. The reason for this new development is still unclear and further evaluation is in hand.

The positive predictive value of an abnormal CMR study was 21.0% for a serious adverse event, whilst the negative predictive value of a normal CMR study was 98.8% for a serious adverse event. Kaplan–Meier curves showed that an abnormal CMR was significantly associated with a lower event-free survival (Fig. 4). Of note, an abnormal CMR was also a significant predictor of events in the subgroup of patients in whom an ICD was implanted, with 10 out of 11 patients with an appropriate ICD discharge presenting with an abnormal CMR study (Fig. 5). Cox proportional models demonstrated that an abnormal CMR study was a significant predictor of the composite end-point (HR 16.1, 95% CI 4.7–55.1, p < 0.001). The risk of an abnormal CMR was compared to traditional clinical parameters. Of the evaluated variables, male gender (HR 4.1, 95% CI 1.4–12.2, p = 0.01), unexplained syncope (HR 2.8, 95% CI 1.1–7.2, p = 0.04), previous cardiac arrest (HR 8.4, 95% CI 1.9–36.5, p = 0.005), and ventricular tachycardia (HR 6.3, 95% CI 2.1–18.7, p = 0.001) were significant predictors of outcomes on univariate analysis. On multivariate analysis, only abnormal CMR study and ventricular tachycardia remained significant predictors of outcomes (Table 4). EPS results were only available for 36 patients in the follow-up cohort, of which 23 were positive. No patients in the EPS negative group had an event, compared to 2/23 (8.7%) in the EPS positive group (chi square p-value = 0.27).

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**Table 2**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total (n = 323)</th>
<th>Normal CMR (n = 242)</th>
<th>Abnormal CMR (n = 81)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.2 ± 15.7</td>
<td>41.1 ± 15.9</td>
<td>45.3 ± 14.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender, male</td>
<td>162 (50.2%)</td>
<td>110 (45.5%)</td>
<td>52 (64.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Palpitation</td>
<td>150 (46.4%)</td>
<td>115 (47.5%)</td>
<td>35 (43.2%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>57 (17.6%)</td>
<td>41 (16.9%)</td>
<td>16 (19.8%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7 (2.2%)</td>
<td>3 (1.2%)</td>
<td>4 (4.9%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Family history of sudden death &lt; 35 years</td>
<td>59 (18.3%)</td>
<td>47 (19.4%)</td>
<td>12 (14.8%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Family history of ARVC</td>
<td>61 (18.9%)</td>
<td>47 (19.4%)</td>
<td>14 (17.3%)</td>
<td>0.67</td>
</tr>
<tr>
<td>TWI V1–V3</td>
<td>36 (11.1%)</td>
<td>23 (9.5%)</td>
<td>13 (16.0%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ventricular extra-systoles</td>
<td>200 (61.9%)</td>
<td>149 (59.5%)</td>
<td>51 (62.9%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>130 (40.2%)</td>
<td>87 (36.0%)</td>
<td>43 (53.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Inducible ventricular</td>
<td>23 (63.9%)</td>
<td>19 (63.3%)</td>
<td>4 (66.7%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Stimulation</td>
<td>92 (34.3%)</td>
<td>44 (22.4%)</td>
<td>48 (66.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal RV on echocardiogram</td>
<td>28 (8.7%)</td>
<td>16 (6.6%)</td>
<td>6 (7.4%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>13 (4.0%)</td>
<td>10 (4.1%)</td>
<td>3 (3.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>24 (7.5%)</td>
<td>16 (6.6%)</td>
<td>8 (10.0%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data is presented as n (%) or mean ± SD. RBBB = right bundle branch block; TWI = T-wave inversion; VE = ventricular extrasystole; VT = ventricular tachycardia; RV = right ventricle.

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**Table 3**

<table>
<thead>
<tr>
<th>CoV (%)</th>
<th>Agreement (%)</th>
<th>Kappa (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDVI (mL/m²)</td>
<td>10.6</td>
<td>–</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>8.7</td>
<td>–</td>
</tr>
<tr>
<td>RWMA (Y/N)</td>
<td>93.3</td>
<td>0.71 (0.001)</td>
</tr>
<tr>
<td>Fat on T1 imaging (Y/N)</td>
<td>90.0</td>
<td>0.29 (0.051)</td>
</tr>
<tr>
<td>Fibrosis on LGE imaging (Y/N)</td>
<td>96.7</td>
<td>0.84 (&lt;0.001)</td>
</tr>
</tbody>
</table>

VT = indexed right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RWMA = regional wall motion abnormalities; LGE = late gadolinium enhancement.
Individual CMR abnormalities were then evaluated for risk. All individual CMR abnormalities were associated with adverse events: increased RVEDVi (HR 8.5, 95% CI 3.5–20.3, \(p < 0.001\)), decreased RVEF (HR 14.0, 95% CI 5.6–35.1, \(p < 0.001\)), regional wall motion abnormalities (HR 9.4, 95% CI 3.7–23.5, \(p < 0.001\)), myocardial fat infiltration (HR 5.0, 95% CI 1.6–15.5, \(p = 0.006\)), and late gadolinium enhancement (HR 19.3, 95% CI 6.6–56.3, \(p < 0.001\)). Kaplan–Meier curves of event-free survival according to the number of CMR abnormalities are shown in Fig. 6. There was a trend towards increased risk of serious events with one CMR abnormality compared to those without (HR 3.9, 95% CI 0.65–23.3, \(p = 0.14\)), and a significantly increased risk of events when presenting with multiple abnormalities (HR 23.0, 95% CI 5.7–93.2, \(p < 0.001\) if two abnormalities; HR 35.8, 95% CI 9.7–132.6, \(p < 0.001\) if three or more abnormalities). Patients with no abnormalities on CMR had an annual incidence rate of the composite end-point of 0.3% per year, whilst patients with 1, 2, and 3 or more abnormalities had annual event rates of 1.1%, 7.6% and 10.9% per year, respectively (Fig. 7).

4. Discussion

Early diagnosis and accurate risk stratification are the most important management strategies in suspected or confirmed ARVC. We conducted a longitudinal study to determine which CMR imaging parameters in a large patient population with suspected ARVC would predict future adverse cardiovascular events. We found that: 1) An abnormal CMR study was a strong predictor of outcomes, and independent of conventional prognostic markers of ARVC; 2) The prognostic value remained significant in the group of patients who underwent ICD implantation; 3) Individual CMR parameters, such as increased RV end-diastolic volume, decreased RV ejection fraction, RV regional wall motion abnormalities, T1 fatty infiltration, and late gadolinium enhancement were all associated with an increased risk of major cardiac events; and 4) Patients with multiple abnormalities were at a greater risk of cardiac events, whilst patients with a normal study had a very low event rate. These data suggest that CMR can be used as a prognostic tool in patients undergoing evaluation for ARVC, and as a guide to subsequent management and surveillance.
4.1. Risk assessment

Male gender, unexplained syncope, previous cardiac arrest and ventricular tachycardia were associated with an increased risk of events. These findings are in keeping with previous studies in patients with documented ARVC [14–17]. But when combining the above risk factors with abnormal CMR on a multivariable risk model, only the latter remained significant. CMR thus provides independent and incremental prognostic information to the more conventional risk markers in patients under evaluation for ARVC.

The risk of events was also evaluated according to the number of abnormalities on CMR. We found that the risk of adverse events increased significantly when multiple abnormalities were present (Fig. 6). The presence of three or more abnormalities identified a particularly high-risk group, with an event rate of around 10% per year (Fig. 7). Our data imply that patients with multiple CMR abnormalities suggesting ARVC should be more closely monitored and with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%. A normal CMR study therefore appears reassuring as it is associated with a lower threshold for ICD implantation. Conversely, the risk of serious adverse events was low in patients with a normal study, with an annual incidence rate of only 0.3% per year, and a negative predictive value for future adverse cardiovascular events of 98.8%.

Despite a significant association with CMR, echocardiography did not reach statistical significance as a prognosticator (HR 2.54, 95%CI 0.98–6.61, p = 0.06). This finding should be put into perspective, since this was a CMR based study and a referral bias may have occurred with echocardiography (some patients were referred to CMR due to borderline echocardiograms). Furthermore, echocardiography was performed in different centres. Imaging acquisition protocols and evaluation of the right ventricle may have been variable as there were no objective cut-offs for morphological abnormalities in the original Task Force criteria. Further work is required to assess the differential benefit of echocardiography versus CMR in risk stratification of patients with suspected ARVC.

4.2. Previous work

These findings extend our knowledge on the prognostic value of CMR in patients with suspected ARVC. Early work by Keller et al. explored the diagnostic and prognostic roles of CMR in 36 patients with suspected ARVC [18]. They found a good diagnostic agreement between CMR and traditional diagnostic tests for ARVC (CMR was positive in 16 out of 18 patients with clinically diagnosed ARVC, and negative in 14 out of 17 patients where ARVC was excluded). Moreover, they demonstrated that a negative CMR was associated with arrhythmia-free survival (log rank p = 0.05). However, this was a small study with a relatively short follow-up (mean follow-up time of 16 months) and only 6 arrhythmic events. Aquaro et al. recently published a prospective CMR study on 440 patients with a single minor criterion of ARVC (> 1000 PVCs of LBBB morphology) [19]. During a mean follow-up of 44 months, 14 major cardiac events occurred. T1 signal alteration, regional wall motion abnormalities, increased RV volumes and reduced RVEF were predictors of the composite end-point. Overall, patients with an abnormal CMR scan had significantly more cardiac events compared to those with a normal CMR scan, and patients with multiple abnormalities were at the highest risk of cardiac events. From frequent ectopy of right ventricular origin, our study expanded inclusion to any ARVC diagnostic criteria, thereby reaching a larger target population.

Table 4

Clinical predictors of composite end-point (univariate and multivariate analyses).

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95.0% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00–1.06</td>
</tr>
<tr>
<td>Gender, male</td>
<td>4.08</td>
<td>1.36–12.2</td>
</tr>
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<td>Palpitations</td>
<td>3.03</td>
<td>0.43–2.50</td>
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<td>Unexplained syncope</td>
<td>2.75</td>
<td>1.05–7.20</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>8.37</td>
<td>1.92–36.5</td>
</tr>
<tr>
<td>Family history of sudden death &lt;35 years</td>
<td>0.20</td>
<td>0.03–1.49</td>
</tr>
<tr>
<td>Family history of ARVC</td>
<td>0.41</td>
<td>0.09–1.76</td>
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<tr>
<td>TWI V1–V3</td>
<td>0.91</td>
<td>0.21–3.93</td>
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<td>Ventricular extrasystoles</td>
<td>2.66</td>
<td>0.89–7.95</td>
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<td>Abnormal RV on echocardiogram</td>
<td>2.54</td>
<td>0.98–6.61</td>
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<td>Abnormal CMR</td>
<td>16.1</td>
<td>4.72–55.1</td>
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</tbody>
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Fig. 6. Kaplan–Meier curves on event-free survival according to number of abnormalities found on CMR.

Fig. 7. Annual rate of serious adverse events according to number of abnormalities found on CMR.

Please cite this article as: Deac M, et al, Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.04.208
Despite the use of broader inclusion criteria, the main results of these studies are similar, thus supporting the use of the CMR for risk stratification in patients undergoing comprehensive work-up for ARVC.

4.3. Tissue characterization

Unlike Aquaro et al., we examined the role of fibrosis – one of the histological hallmarks of ARVC – on outcomes, using the late gadolinium enhancement (LGE) technique. Gadolinium-based contrast agents act as extracellular tracers that accumulate in areas of increased interstitial expansion such as myocardial fibrosis. The concept of LGE representing fibrous replacement was initially introduced by Tandri et al. [6]. In his original study, LGE was present in 8 out of 12 patients with ARVC, usually in the subtricuspid area, and also in the anterior wall and apex, RV side of the septum, and in the RVOT. A subsequent study by our group showed that LGE was present in 22 out of 28 gene-positive ARVC patients, suggesting that LGE may allow detection of the disease in earlier stages than the conventional Task Force criteria [7]. More recent studies showed LV LGE in a high proportion of patients with ARVC, usually presenting in a mid-wall and epicardial pattern in the inferior and inferolateral walls, but in more severe cases circumferentially around the LV free wall [20,21]. LGE was shown to be associated with inducible ventricular stimulation in a relatively small population of patients with documented ARVC [6]. In this study, the presence of LGE was a strong predictor of outcomes. One potential explanation is that myocardial fibrosis can act as a substrate for ventricular arrhythmias, in line with previous studies on dilated cardiomyopathy and coronary artery disease [22,23]. LGE appears more reproducible and easier to interpret than fatty infiltration on T1 imaging. Only three patients in this study had non-diagnostic information from LGE, whilst 21 patients had non-diagnostic T1 images. Furthermore, LGE was useful to provide an alternative diagnosis in 8 patients, leading to a different management pathway. The current document on standardized protocols endorsed by the Society for CMR (SCMR) considers LGE imaging as an optional sequence in the evaluation of ARVC [24]. Given the established diagnostic role in addition to the potential prognostic role documented in this study, our study suggests a benefit in performing LGE imaging in all patients with suspected or confirmed ARVC.

Another histological characteristic of ARVC is myocardial fat replacement. Initial CMR studies documented the presence of high T1 signal indicating fat infiltration within the myocardium in up to 75% of patients with ARVC compared to none in controls [25]. In this cohort, fatty infiltration by CMR was associated with outcomes, in keeping with the results by Aquaro et al. [19]. However, the association with events was not as strong as the other CMR parameters. This modest prognostic value may be due to the lower reproducibility observed in this study, underpinning the limitations of fat evaluation by CMR in ARVC. Detection of fat can be extremely challenging as underlined by previous studies showing to be less reliable than other morphological markers of ARVC [7,26,27]. The same diagnostic caveat is also present on histological examination, where normal epicardial fat deposition can be mistaken for pathological myocardial fat infiltration. For histological evaluation of ARVC, fat deposition is only relevant for diagnosis if accompanied by myocardial fibrosis and myocyte degeneration. Thus, LGE may represent a better CMR marker of fibrofatty infiltration than T1 imaging alone. Fibrous replacement of the myocardium is also believed to be more arrhythmogenic than fat infiltration [28]. Nonetheless, studies correlating in vivo tissue characterization by CMR with histology are lacking in ARVC and further investigation is still needed.

4.4. Limitations

This study reflects a routinely encountered cohort of patients referred to CMR for evaluation of ARVC. By representing a ‘real-life’ cohort, the study population was relatively heterogeneous in nature, ranging from patients with no structural heart disease to patients with intermediate phenotypes and overt ARVC. The rationale behind the enrolment was to include patients with early concealed forms of the disease that would be detected by CMR but otherwise missed by the conventional diagnostic algorithms for ARVC [7]. Patient selection was based on the original Task Force criteria at the time of enrolment, but the final follow-up and diagnostic analysis was performed after publication of the updated diagnostic criteria [3]. From an imaging perspective, the revised criteria appear less sensitive for the diagnosis of this condition [29]. Combined with the lack of diagnostic criteria for non-classical forms of ARVC with biventricular or predominant LV involvement, the overall prevalence of ARVC in this cohort may have actually been underestimated.

This was an observational study with retrospective event collection because a prospective follow-up is difficult to perform in a relatively uncommon condition with a low recorded event rate. Contrast imaging was performed in about two-thirds of patients because gadolinium only became part of the routine assessment of ARVC in our institution after 2003. However, there was no significant demographic difference before and after implementation of routine contrast imaging, therefore limiting any potential selection bias.

5. Conclusions

Comprehensive CMR evaluation provides important and incremental prognostic information in patients with suspected ARVC. A normal CMR study predicts a low incidence rate of future events. Conversely, detection by CMR of multiple morphological abnormalities suggesting ARVC identifies a group of patients at a particularly high risk of serious events, and more aggressive management, including ICD implantation should be considered in this setting.

Conflicts of interest

Relationship with industry: DJP is a consultant to Siemens, and a director of Cardiovascular Imaging Solutions. SKP has received Honoraria for talks from Bayer-Schering. No other conflicts of interest.

Acknowledgements

This project was supported by the NIHR Cardiovascular Biomedical Research Unit of Royal Brompton and Harefield NHS Foundation Trust and Imperial College London.

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