Prognostic value of myocardial scar in ischaemic and non-ischaemic cardiomyopathy using cardiac magnetic resonance imaging

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Abstract

Aim: The aim of this research was to evaluate the prognostic value of myocardial scar using cardiac magnetic resonance (CMR) imaging in patients with ischaemic cardiomyopathy (ICM) and non-ischaemic cardiomyopathy (NICM).

Methods: One hundred and fifty-four patients with either ICM or NICM underwent CMR with late gadolinium enhancement sequences for assessment of left ventricular ejection fraction (LVEF), and detection and quantification of any myocardial scar using three methods: manual, number of segments involved, and percentage of scarred myocardium. Patients were followed up for at least six months for clinical cardiac events.

Results: Patients were divided into two groups: group I, patients with ICM (58%) and group II, those with NICM (42%). Clinical presentation ranged from eventless (10%) to chest pain (18%), heart failure (15%), hospitalisation (35%), syncope (1%), ventricular tachycardia (≤ 1%) and cardiac arrest (≤ 1%). The scar mass was larger in size in group I (17 ± 15%) than in group II (8 ± 13%). A direct relationship was observed between scar size and event severity (p < 0.001). An inverse relationship between LVEF and event severity was found in group I (p < 0.001) but not in group II (p = 0.128).

Conclusion: Myocardial scar size was a strong predictor of clinical outcome in both the ICM and NICM patients. LVEF was less reliable in predicting morbidity in cardiomyopathy patients.

Keywords: ischaemic cardiomyopathy, non-ischaemic cardiomyopathy, cardiac MRI, myocardial scar

Cardiovascular Topics
with ICM and NICM and compare it to the prognostic value of the LVEF in the same study population.

Methods

This study included 154 patients who were diagnosed to have cardiomyopathy (both ischaemic and non-ischaemic) using cardiac MRI (1.5 tesla). The patients were either referred from heart failure clinics or recruited directly after having been diagnosed by cardiac MRI.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol got the approval of the Committee of Ethics of the Alexandria University.

CMR was performed using the 1.5-T machine. Sequences were ECG-triggered and performed in breath-hold technique using a body array coil. Myocardial function was assessed with cine steady-state free-precession (SSFP) pulse sequences that were acquired in stacks of short-axis slices covering the whole left ventricle with eight to 10 contiguous sections. LGE was acquired 10 minutes after intravenous gadolinium contrast (0.2 mmol/kg) by using a gradient-spoiled turbo fast low-angle shot sequence with phase-sensitive inversion recovery technique in four- and two-chamber views and a series of left ventricular short axes (section thickness 6 mm).

The cardiac MRI study analysis included (1) ventricular function assessment (LVEF) though volume measurements in short-axis cine images; (2) detection of any myocardial scar or fibrosis using short-axis, two-, three- and four-chamber LGE images; (3) quantification of myocardial scar/fibrosis using three methods: manual quantification of the LGE mass in each slice of the short-axis LGE sequence; number of segments involved in the scar tissue (segments involving LGE); percentage of the scarred myocardium (summation of the percentage of the scarred myocardium in each segment of the 17 myocardial segments in relation to the total left ventricular mass).

All 154 patients were followed up for at least six months for any clinical cardiac events. These events were scaled according to severity, from one (less severe) to seven (most severe); ranging from mild chest pain (non-acute coronary syndrome), mild dyspnoea (New York Heart Association stage I–II), and including hospital admission due to decompensated heart failure and up to syncope, documented ventricular arrhythmia and sudden cardiac arrest/death, respectively. Follow-up details were collected from hospital records and arranged phone calls with patients.

Statistical correlation between the amount of the scarred myocardium in both ICM and NICM patients and the severity of the clinical events during the period of the follow up was performed. If any patient had experienced more than one event, the most serious one was considered the main event for this patient. Details of clinical events were collected from hospital records. Additional phone calls were arranged to get more details about the patient’s symptoms.

Statistical analysis

Data were fed into the computer and analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov test was used to verify the normality of distribution of variables. The Spearman coefficient was used to correlate between quantitative variables. Significance of the obtained results was judged at the 5% level.

Results

One hundred and fifty-four patients were included in the study, and 87 patients (56%) were male and 67 (44%) were female, with a mean age of 61 ± 15 years (range 20–87). The time of the clinical follow up was variable, with a minimum of six months and a mean of 10 months (from six to 40 months).

Our patients were divided into two groups; 89 (58%) were diagnosed with ICM and 65 (42%) with NICM. The NICM subgroup included a variety of different aetiologies of cardiomyopathies: 41 patients were diagnosed to have dilated cardiomyopathy (DCM), seven with Takotsubo cardiomyopathy, five with left ventricular non-compaction, four with apical non-obstructive hypertrophic cardiomyopathy (HCM), three with amyloidosis, two with sarcoidosis, two with arrhythmogenic left ventricular dysplasia and one patient with endomyocardial fibrosis. Of the 154 patients, 52 (34%) had LVEF < 45% (28 patients in group I and 24 in group II) and 102 (66%) patients had LVEF ≥ 45% (61 patients in group I and 41 in group II).

All the 154 patients were followed up clinically for at least six months. The clinical presentation ranged from eventless (no events) in 16 patients (six in group I, 10 in group II), chest pain in 28 (18%) patients (19 in group I, nine in group II), heart failure in 23 (15%) (12 in group I, 11 in group II), hospitalisation in 54 (35%) patients (35 in group I, 19 in group II), syncope in 14 (1%) (six in group I, eight in group II), ventricular tachycardia in nine (< 1%) patients (five in group I, four in group II) and cardiac arrest in 10 (< 1%) patients (six in group I, four in group II).

Our main concern in this study was to determine whether there was a relationship between the scar size detected in the LGE CMR and the severity of clinical presentation of the patient during the follow up.

In our study, a direct relationship between the absolute size of the myocardial scar (g) and event severity was observed (p < 0.001, r = 0.464), as shown in Table 1 and Fig 1. When the two subgroups were compared, the scar mass was larger in size in group I (19.5 ± 18.9 g) than in group II (11.3 ± 19.9 g) but still with a linear relationship between scar size and event severity (p < 0.001) in both groups (Fig. 1).

The size of the scar was also assessed by the total number of segments involved in the scar. Again, there was a significant direct relationship between the number of segments involved in this scar and event severity in both subgroups (group I, p < 0.001, r = 0.490; group II, p < 0.001, r = 0.536). The third method to evaluate the myocardial scar mass was through calculation of the percentage of myocardial scar to the total myocardial mass (by estimating the percentage of scar tissue in each segment of the 17 myocardial segments separately, each myocardial segment representing 1/17th of the total myocardial mass). The mean scar percentage was 17 ± 15% in the ICM patients and 8 ± 13% in the NICM patients. There was also a direct relationship observed between the estimated percentage of scarred myocardium and event severity (group I, p < 0.001, r = 0.468; group II, p < 0.001, r = 0.558) (Fig. 2).
Regarding the left ventricular systolic function assessed by LVEF, there was an inverse relationship between the LVEF and event severity in the ICM group ($p = 0.013$, $r_s = -0.263$) (Fig. 3). This was different from the results of the NICM group where there was no significant correlation between the LVEF and event severity ($p = 0.128$, $r_s = 0.180$).

**Discussion**

Many of the recent research studies concerned with myocardial scar were designed to assess the presence or absence of this scar and its relationship with sudden cardiac arrest and/or malignant ventricular arrhythmias, hence the indication for implantable cardioverter–defibrillator (ICD) insertion, paying less attention to the rest of the clinical spectrum of the outcome. In our study, we were not only interested in sudden cardiac arrest as the main outcome. The wider spectrum of clinical events is thought to provide more data on expected clinical pattern, hence, treatment plans and expected quality of life in cardiomyopathy patients.

A linear relationship was clearly observed between the size of the myocardial scar (using any of the three methods) and the severity of the clinical event. More serious cardiac events such as hospitalisation due to heart failure, serious arrhythmias and "Table 1. Analysis of scar mass, actual number of scar segments, percentage of scar and LVEF in groups I and II"

<table>
<thead>
<tr>
<th>Event</th>
<th>Scar mass (g), mean ± SD</th>
<th>Number of scar segments, mean ± SD</th>
<th>Percentage of scar, mean ± SD</th>
<th>LVEF (%), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total*</td>
<td>Group I*</td>
<td>Group II*</td>
<td>Total*</td>
<td>Group I*</td>
</tr>
<tr>
<td>No events</td>
<td>0.3 ± 0.4</td>
<td>0.4 ± 0.4</td>
<td>0.7 ± 0.7</td>
<td>0.8 ± 0.8</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.9 ± 0.8</td>
<td>1.3 ± 0.7</td>
<td>0.2 ± 0.4</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.4 ± 1.9</td>
<td>2.0 ± 1.8</td>
<td>0.8 ± 1.8</td>
<td>2.1 ± 2.2</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>4.1 ± 3.0</td>
<td>4.7 ± 2.9</td>
<td>2.8 ± 3.3</td>
<td>5.5 ± 3.5</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.4 ± 1.2</td>
<td>1.9 ± 1.2</td>
<td>1.0 ± 1.2</td>
<td>2.5 ± 1.9</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1.7 ± 1.3</td>
<td>1.6 ± 1.2</td>
<td>1.8 ± 1.5</td>
<td>2.4 ± 1.7</td>
</tr>
<tr>
<td>Arrest</td>
<td>2.7 ± 1.8</td>
<td>3.3 ± 1.8</td>
<td>1.9 ± 1.8</td>
<td>3.3 ± 1.7</td>
</tr>
</tbody>
</table>

*Statistical significance with event severity.
sudden cardiac arrest were detected more often in patients with a larger scar size in both groups ($p < 0.001$) (Figs 4–6).

It was observed that serious cardiac events were less often seen in patient with a mean scar mass of $<5.4–8.4\%$. On the contrary, patients who had experienced sudden cardiac arrest had a mean scar mass of $15.9\%$ and patients with ventricular tachycardia had a mean scar mass of $9.8\%$ (Table 1). It was also interesting that hospitalisation with decompensated heart failure was significantly more frequent in patients with a high scar mass, especially in ICM patients with a mean scar mass of $27.9\%$. This may be explained that the scar mass in ICM patients was directly reflecting the severity of the baseline coronary artery disease and the number of territories involved. Another finding that may support this theory is that the mean LVEF for those patients was $<45\%$.

Neilan et al. demonstrated that for every 1% of left ventricular mass increase in scar size, the risk of cardiovascular death or ventricular arrhythmia increased by 15%. This relationship was similar whether scar size was measured using the 2-SD method (hazard ratio (HR) 1.15; 95% confidence interval (CI): 1.12–1.18) or the FWHM method (HR 1.16; 95% CI: 1.12–1.20).

When only arrhythmic events were considered, the extent of the scar was again associated with higher event risk (HR 1.17 for each 1% absolute increase in scar size; 95% CI: 1.12–1.22). Similar results were reported by Gulati et al., where for each percentage scar extent, the risk of all-cause mortality was increased by 11% (HR 1.11; 95% CI: 1.06–1.16) and the risk for arrhythmic events was increased by 10% (HR 1.10; 95% CI: 1.05–1.16).

Li et al. aimed to develop a risk score [LGE-based prediction of sudden cardiac death (SCD) risk in non-ischaemic dilated cardiomyopathy (NIDCM) (ESTIMATED)] based on LGE in CMR to predict SCD in patients with NIDCM and LVEF $\leq 35\%$. They followed up 395 patients with NIDCM for three years for SCD events. The estimated score (constructed by the LGE extent $>14\%$, syncope, atrial flutter/fibrillation, non-sustained ventricular tachycardia, advanced atrioventricular block, and age $\leq 20$ or $>50$ years) showed good calibrations for SCD prediction. From the score, 20.3% of primary-prevention patients were categorised as high risk (≥ three points), 28.1% as intermediate risk (two points) and 51.6% as low risk (zero to one point) for three-year SCD events (45.9 vs 20.1 vs 5.1%, $p < 0.001$). The three-year SCD events were also well in agreement with the score stratification in patients without ICDs. Their study suggested LGE-based (ESTIMATED) risk score to be validated in providing refined SCD prediction. The score may help to identify candidates for primary-prevention ICDs in patients with NIDCM.
Our study included both the ischaemic and non-ischaemic spectrum, studied independently and also compared to each other. Moreover, the follow up included a wider spectrum of clinical events ranging from mild chest pain or shortness of breath, passing through hospitalisation due to decompensated heart failure and up to malignant arrhythmia and sudden cardiac arrest. We were concerned about the clinical pattern of the patients regarding their morbidity, hospitalisation and quality of life.

The mean LVEF was 51 ± 14% (18–77) in group I (32% of group I with LVEF < 45% and 69% with LVEF > 45%) and 48 ± 16% (9–77) in group II (37% of group II with LVEF < 45% and 63% with LVEF > 45%). There was a statistically significant linear relationship between left ventricular systolic dysfunction represented by LVEF and event severity in group I ($r_s = 0.263^*$, $p < 0.013^*$).

On the other hand, for group II patients, there was no clear relationship between LVEF and event severity ($r_s = 0.180$, $p < 0.150$). In this non-ischaemic group, the main predictor of cardiac events was scar mass. For example, in the four patients in group II who experienced sudden cardiac arrest, the LVEF was > 45% but with a high scar mass average (13.99 ± 13.77 g).

It was also observed in group I that the lower LVEF was more linked with hospitalisation due to decompensated heart failure (63% of the hospital admissions had LVEF < 45%). On the other hand, most of the patients with no events or mild chest pain or dyspnoea had LVEF > 45%. This could be explained by the fact that in ischaemic patients, the amount of scarred myocardium was directly linked to the severity of the underlying coronary artery disease, and the amount of scar mass and its distribution may also indicate the number of coronary territory affected.

In non-ischaemic patients, the preserved LVEF is misleading because it does not indicate the degree of underlying myocardial pathology. However, LGE in cardiac MRI is more precise in tissue characterisation and spotting unhealthy myocardium that is usually a substrate for serious arrhythmogenic events and subsequently sudden cardiac arrest, even in cases of preserved LVEF.12

In the report by Dokainish et al.,13 they had a similar outcome to ours when they evaluated the prognostic implications of left ventricular systolic and diastolic dysfunction early post-acute ST-segment elevation myocardial infarction. Patients with LVEF ≤ 45% and restrictive diastolic function (RDF) were at greatly increased risk of major adverse cardiovascular events (MACE) (HR 8.85, 95% CI: 4.21–18.60) compared to patients with LVEF ≥ 45% and without RDF. RDF remained a strong predictor for MACE in patients with LVEF ≥ 45% (HR 4.38, 95% CI: 1.52–12.60), and in multivariate models adjusted for LVEF, left ventricular end-systolic volume and clinical variables.
Fig. 4. CMR LGE images. A: two-chamber, B: four-chamber, C: three-chamber long axis views, D: basal, E and F: mid-cavity short-axis views showing extensive mid-myocardial fibrosis for a patient with arrhythmogenic left ventricular cardiomyopathy, presented with multiple syncopal episodes. The Holter monitor showed frequent multifocal ventricular ectopic beats. LVEF was 54%, scar mass was 9.9 g, representing 16% of the myocardial mass detected in eight segments.

Fig. 5. CMR images. A and B: four-chamber and short-axis cine images, C and D: four-chamber and short-axis LGE of left ventricular non-compaction in an asymptomatic patient (nine-month follow up) with no myocardial scar/fibrosis. LVEF was 47%.

Fig. 6. CMR images. A and B: short-axis and two-chamber cine images, C and D: short-axis and two-chamber LGE images showing transmural myocardial scar of the basal and mid-cavity inferior and inferolateral segments (four segments), partially involving both papillary muscles. The evaluated myocardial scar mass was 28 g, representing 24% of the myocardium for a patient admitted with heart failure symptoms.
Regarding non-ischaemic cardiomyopathy, Ge et al. investigated whether structural abnormality on CMR represented by LGE may be a predictor of MACE in patients with non-sustained ventricular tachycardia (NSVT) and ventricular tachycardia (VT)/SCD. They studied 651 patients (age 54 ± 15; 61% male) referred to CMR for ventricular arrhythmia, who were divided into two groups according to the presence of NSVT (53%) or sustained VT/aborted SCD (47%). MACE was a composite of cardiovascular death, a need for heart transplantation or left ventricular assist device and recurrent VT/ventricular fibrillation needing therapy. The mean LVEF was 54 ± 13% and LGE was present in 39% of patients (mean 9.5 ± 8%).

A structurally abnormal heart, defined by LGE, abnormalities in wall motion or impaired systolic function was observed in 52% of patients (n = 336). A change in diagnostic impact based on CMR took place for 27% of patients with NSVT versus 40% of patients with VT/SCD (p < 0.001). A total of 122 patients experienced MACE during the follow-up period (median, 3.6 years). Structural abnormality detected on CMR was found to be an independent predictor of MACE (HR 3.65; 95% CI: 2.09–6.27; p < 0.001).

Although each of the three methods used to quantify the myocardial scar using LGE in CMR has a different concept to calculate the size of the scar, they all showed comparable results. The manual method is a commonly used technique, however, it is extremely time consuming. The second method, using the total number of segments involving any LGE is theoretically less accurate as it considers one segment affected even if the late enhancement is focal or minimal. On the other hand, it is the least time-consuming method as it gives only a general impression of how many of the myocardial segments include scarred tissue. However, the third method, summation of the percentage of the scarred myocardium in each segment of the 17 myocardial segments, is less time consuming than the manual one, with considerable accuracy in representing how much of the myocardium is unhealthy.

Many other methods were tested and compared for accuracy in quantifying myocardial scar. Flett et al. studied the reproducibility of LGE quantification techniques in three different pathological conditions: acute myocardial infarction, chronic myocardial infarction and HCM, using seven techniques. These were manual quantification, automatic methods including thresholding by 2-, 3-, 4-, 5- or 6-SD above remote myocardium, and the FWHM technique. They concluded that regardless of the underlying disease, the FWHM technique for LGE quantification gave mean LGE volume results similar to manual quantification and it was statistically the most reproducible, reducing the required sample sizes by up to a half.

Another study by Gao et al. using automatic thresholding measured a 50% larger scar size going from 5-SD to 2-SD thresholds above remote myocardial signal intensity. Neilan et al. found that scar size was, on average, 50% greater using the 2-SD technique versus the FWHM technique (9 ± 5% by 2-SD method vs 6 ± 4% by FWHM method), however, there was close correlation between both the measurements (r = 0.92, p < 0.001), and more importantly, both methods of quantification showed robust prognostic association.

Therefore, despite the different ways used to quantify myocardial scar, manual assessment is considered one of the most accurate methods. However, no one specific method has been agreed on to be the standard yet.

The small number of patients included in our study, especially in each type of cardiomyopathy, is one of the limitations in our study. In addition, longer follow-up time would have added more significant predictive value.

Conclusion
Myocardial scar/fibrosis using CMR is a reliable parameter that can reflect the degree of diseased myocardium. The amount of scarred or fibrosed myocardium is found to be directly linked to the severity of the clinical event in both ICM and NICM patients. The larger the scar size, the more severe was the clinical event, even with preserved LVEF. Therefore, quantification of myocardial scar/fibrosis could be used as a predictor for cardiac events, hospitalisation and SCD.

LVEF is not always linked with severity of the cardiac event, especially in NICM patients. Low LVEF was mainly linked with hospitalisation in both ICM and NICM patients.

References


