Myocardial scar extension detected by late Gadolinium enhancement-cardiovascular magnetic resonance (LGE-CMR) for arrhythmic risk stratification of HCM patients

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Purpose

Hypertrophic cardiomyopathy (HCM) has been largely regarded to be associated with disability and death in patients of all ages, and annual mortality rates is as high as 3% to 6%. [1]

Sudden cardiac death (SCD) in young people is the most devastating component of its natural history and it's increasingly recognized as an initial presentation in young HCM patients [2,3]. Ventricular tachyarrhythmia (VT) seem to be the primary cause of SCD [4]

Irreversible myocardial replacement scarring is recognized as the anatomical and electrophysiological basis of VT and most of the arrhythmic events because of the altered impulse conduction and it's associated with the occurrence of VT and SCD in patients with HCM [5]

Late gadolinium-enhanced cardiovascular magnetic resonance (LGE-CMR) enables detection and quantification of myocardial damage in HCM patients.

The prediction and prevention of SCD due to VT is of paramount importance in the management of HCM patients [6 - 8]

Implantable cardioverter-defibrillators (ICDs) correct potentially lethal arrhythmias in HCM, but there aren't currently defined criteria for the selection of patients who would benefit from ICD implant

The selection of patients for ICD implantation is presently performed on the bases of different techniques (24 hours ECG-Holter monitoring, history of SCD) with a low predictive accuracy [9]

The aim of the present study is to investigate the role of myocardial fibrosis detected by LGE-CMR as a potential arrhythmogenic substrate in HCM, throughout the association between LGE extension and the occurrence of ventricular tachyarrhythmias and implantable cardioverter defibrillator shock (ICDs).
Methods and Materials

Study population:

90 consecutive patients (mean age 58.4±15.3 years, range 15-79; 60 male and 30 female) with a diagnosis of HCM underwent LGE-CMR between August 2005 and August 2012 at the Radiology Institute of the University Hospital of Modena, Italy. The clinical features of the study population are summarized in figure 1.

The local ethical committee at our institution approved the study, and informed consent for the LGE-CMR protocol was obtained from all patients.

The exclusion criteria adopted to select the study population were:

- Patients with clinical history of atherosclerotic coronary artery disease or another disease likely to cause hypertrophy;
- Patients with Implantable Cardiac Defibrillator (ICD) and patients submitted to alcohol septal ablation or surgical septal myomectomy procedures;
- Patients with a severe renal impairment (GFR<30mL/min/1.73m²);
- Patients with arrhythmia preventing proper ECG-gating.

LGE-CMR acquisition:

LGE-CMR examinations were performed on 1.5 Tesla scanners (Achieva, Philips Medical System, Best, The Netherlands). A dedicated five-element, phase-array body coil was used. Images were acquired during repeated end-expiratory breath-old of 10-15 s, depending on the heart rate.

The study protocol was:

- Balanced Turbo Field Echo (b-TFE) sequence breath-hold in short-axis view (8 mm): to evaluate myocardial thickness and global cardiac function (figure 2).
- 3D inversion-recovery TFE (IR-TFE) breath-hold in short-axis view, 15 minutes after intravenous administration of 0.1 mmol/kg Gd-DOTA based contrast agent (Gadolinium-DOTA, Dotarem, Guerbet S.A., Cedex, France): to detect and quantify myocardial damage (figure 3).

The inversion recovery time was adjusted per patient to optimally null the signal from normal myocardium (typically 230-350 ms).

Total acquisition time averaged 40 minutes.
**Images analysis, determination of ventricular and atrial parameters and LGE quantification:**

Cine and contrast-enhanced images were evaluated separately by the consensus of two experienced observers and their analysis was blinded from the clinical and ECG data of HCM population.

Volume and mass measurements were assessed off-line from the images obtained in the short-axis by using a dedicated commercially available software (ViewForum 3.2, Philips Medical System, Best, The Netherlands). All volumes and mass measurements were obtained by applying the Simpson's method and were indexed to body surface area (figure 4).

The LGE was assessed automatically on short-axis slices by the 2 independent observers. The mean signal intensity (and SD) of normal myocardium is calculated and a threshold # 6 SD exceeding the mean signal of a area of non-enhanced myocardium was used to define areas of LGE. Such quantitative scar analysis has been shown to be highly reproducible in a previous study [10].

Areas of artefact will be excluded from the analysis by manually adjusting the individual contours (figure 5).

Total volume of LGE (measured in grams) was expressed as a proportion of total indexed end-diastolic left ventricular mass (IEDLV mass).

**Electrocardiographic analysis and arrhythmia monitoring:**

Patients underwent standard ECG and 24 h ECG Holter-monitoring once a year.

The occurrence of VT and any other arrhythmia was documented by performing one of these two examination. Presence of VT (sustained or non-sustained), was defined as: three or more consecutive ventricular beats at a rate of 120 beats/ min [6].

**Follow up:**

All patients underwent successfully CMR examination.

Occurrence of VT (sustained and non-sustained), ICD implant and ICD shocks during 40.2±11.1 months of follow-up were recorded by interviewing patients and their cardiologists.

Only new events from the time of recruitment were considered in the primary or secondary outcomes.
**Statistical analysis:**

The statistical correlations between extension of LGE and the occurrence of VT and ICD shock was performed with university and multivariate analysis. All results were considered statistically significant when p<0.05.
<table>
<thead>
<tr>
<th>Demographics and clinical parameters</th>
<th>Value (n.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 patients</td>
<td>Value (n.)</td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>5.4±15.3</td>
</tr>
<tr>
<td>Males (%)</td>
<td>60 (60.6)</td>
</tr>
<tr>
<td>Familiar form of HCM (%)</td>
<td>34 (37.8)</td>
</tr>
<tr>
<td>Dyspnea (%)</td>
<td>34 (37.8)</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>14 (15.5)</td>
</tr>
<tr>
<td>NYHA III-IV Class (%)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>LVOT Obstruction (%)</td>
<td>34 (37.8)</td>
</tr>
</tbody>
</table>

**Fig. 1:** Demographic and clinical characteristics of the study population.

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Fig. 2: b-TFE sequence breath-hold in short-axis view in a patient with HCM.

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Fig. 3: IR3D-TFE breath-hold in short-axis view in the same patients with HCM.

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Fig. 4: LV masses and volumes calculated with Simpson's method.

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Fig. 5: LGE extension quantified with automatical method (6SD).

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Results

The CMR parameters of the study population are collected in figure 6. The mean IEDLV mass was $89.5\pm28.4\ \text{g/m}^2$. On LGE-CMR, 70 (80%) patients showed myocardial scar and the mean LGE% was $8.11\pm6.63$ of IEDLV mass.

During $40.2\pm11.1$ months follow-up period we recorded:

- 18 (20%) NSVT;
- 10 (11.1%) SVT;
- 9 (10%) patients underwent ICD implantation and 4 of them experienced one or more appropriate ICDs.

We found a statistically significant correlation between LGE% and FA, NSVT and SVT (figure 7).

LGE% was significantly higher in patients who exhibited NSVT and SVT than in patients who did not: $[11.6\pm7.5]$ vs. $[4.6\pm5.6]$, $P=0.00001$ (Figure 8, 9).

However, also patients who presented SVT exhibited a significantly higher LGE% compared to those who didn't experienced this arrhythmic event: $[13.9\pm7]$ vs. $[5.9\pm5.1]$, $P=0.00001$ (Figure 10, 11).

There was no statistically significant relationship between LGE extension and ICDs: $P=0.075$.

Although it wasn't found a statistically significant correlation, patients who reported ICD discharges during the follow up displayed significantly more LGE% compared to patients without any ICD shock ($13.9\pm7$ vs. $5.9\pm5.1$; $p$-value: 0.075) (Figure 12). This result may be explained by the small number of patients with ICD in the study population (in particular those who had ICD discharges) and by the relatively short period of clinical follow-up. This result needs to be explored in a longer term follow-up studies with greater number of patients implanted with ICD and with more clinical risk factors.
**Fig. 6:** LGE-CMR parameters of the study population.

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**Fig. 7:** Correlation between LGE extension and arrhythmic events in HCM patients of the study population.

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<table>
<thead>
<tr>
<th>LGE extension VS. Arrhythmic events</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-Sustained Ventricular Tachyarrhythmia</td>
<td>0.00001</td>
</tr>
<tr>
<td>Sustained Ventricular Tachyarrhythmia</td>
<td>0.00001</td>
</tr>
<tr>
<td>ICD shock</td>
<td>0.075</td>
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<tr>
<td>Sudden cardiac death</td>
<td>n.s.</td>
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</tbody>
</table>
### CMR parameters and NSVT

<table>
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<tr>
<th>90 patients</th>
<th>No NSVT</th>
<th>NSVT</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>EF (%)</strong></td>
<td>62.6±10.6</td>
<td>65±9.6</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Stroke volume index (ml/m²)</strong></td>
<td>51.1±11.7</td>
<td>50.5±11</td>
<td>0.42</td>
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<tr>
<td><strong>ED volume index (ml/m²)</strong></td>
<td>78.8±29.4</td>
<td>78.9±17.7</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>ES volume index (ml/m²)</strong></td>
<td>32±15.1</td>
<td>28.7±17.9</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>ED wall mass index (g/m²)</strong></td>
<td>87±21.9</td>
<td>90.2±30</td>
<td>0.33</td>
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<tr>
<td><strong>LGE%</strong></td>
<td>4.6±5.6</td>
<td>11.6±7.5</td>
<td><strong>0.0001</strong></td>
</tr>
</tbody>
</table>

**Fig. 8:** Correlation between NSVT and LGE-CMR parameters.

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**Fig. 9:** Graphic to explain the different LGE extension between the 2 population of patients (who didn't present and who presented NSVT during the follow up).

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### CMR parameters and SVT

<table>
<thead>
<tr>
<th></th>
<th>No SVT</th>
<th>SVT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 patients</td>
<td>EF (%)</td>
<td>63.7±10</td>
<td>64.6±9.8</td>
</tr>
<tr>
<td></td>
<td>Stroke volume index (ml/m³)</td>
<td>54.3±9.1</td>
<td>50.1±11.3</td>
</tr>
<tr>
<td></td>
<td>ED volume index (ml/m³)</td>
<td>86.1±35.6</td>
<td>77.8±17.6</td>
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<tr>
<td></td>
<td>ES volume index (ml/m³)</td>
<td>34.5±18</td>
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<td></td>
<td>ED wall mass index (g/m²)</td>
<td>93.4±26</td>
<td>89±28.8</td>
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<tr>
<td></td>
<td>LGE%</td>
<td>5.9±5.1</td>
<td>13.9±7</td>
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</tbody>
</table>

**Fig. 10:** Correlation between SVT and LGE-CMR parameters.

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Fig. 11: Graphic to explain the different LGE extension between the 2 population of patients (who didn't present and who presented SVT during the follow up).

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Fig. 12: Graphic to explain the different LGE extension between the 2 population of patients (who didn't present and who presented ICD shock during the follow up).

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Conclusion

Extension of fibrosis on LGE-CMR predicts the occurrence of NSVT and SVT in HCM patients.

LGE-CMR has a predictive value and it can be used to stratify patients with HCM by risk of arrhythmic events on the basis of LGE%.

Therefore, the use of LGE-CMR may be relevant to influence therapeutic strategies, in particular to clinical decision making and considerations for prophylactic ICD therapy in selected patients with HCM.
References


Personal Information

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