Role of myocardial scar location detected by late Gadolinium enhancement-cardiac magnetic resonance (LGE-CMR) to predict ventricular tachyarrhythmias in HCM

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Purpose

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by abnormal thickening of the left ventricular wall in the absence of increased afterload [1]. The distribution of the thickening is heterogeneous, ranging from involvement of the basal anterior septum (95% of cases) to involvement of the left ventricular apex to complete, symmetrical and concentric hypertrophy.

Cardiac magnetic resonance imaging has emerged as a powerful non-invasive technique to depict the morphology of the right and left ventricles and to assess regional and global ventricular function [2].

Furthermore the recent introduction of late gadolinium enhancement (LGE-CMR) allows the accurate detection of myocardial fibrosis in HCM [3].

The abnormalities of myocardial tissue (disarray, infarct and fibrosis) can cause in HCM patients rhythm disorders.

Sudden cardiac death (SCD) is increasingly recognized as an initial presentation in young HCM patients [4, 5]. The primary cause of SCD is often ventricular tachycardia or fibrillation (VT/VF) [6]. Scarred myocardium is recognized as the anatomic and electrophysiological substrate for the occurrence of VT (non-sustained and sustained) [7].

The American Heart Association (AHA) Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging defined standardized myocardial segmentation for CMR imaging. This association recommends a 17-segment model of the left ventricle as an optimally weighted approach for the visual interpretation of regional left ventricular (LV) abnormalities [8].

The aim of this study is to determine the prognostic value of LGE-CMR to detect myocardial fibrosis location and its relationship with the occurrence of ventricular tachyarrhythmias in HCM patients.
Methods and Materials

Study population:

In this non-randomized, prospective study, we enrolled 90 patients (60 males and 30 females) whose ages ranged from 14 to 79 years (mean age 58.4±15.3 years ) with a diagnosis of HCM. The clinical and demographic features of the study population are showed in figure 1.

HCM is diagnosed on the basis of clinical assessment, echocardiography, coronary angiography (in case of any doubt of ischemic disease) and ECG-Holter-monitoring during 24 h. All patients had positive findings for hypertrophic cardiomyopathy on transthoracic echocardiography and CMR was used to confirm diagnosis and to quantify myocardial damage, detected by LGE imaging.

All patients underwent 1.5T LGE-CMR between August 2005 and September 2012, at the Radiology Institute of the University Hospital of Modena and Reggio Emilia, Italy.

We excluded patients with a clinical history of atherosclerotic coronary artery disease and those who were implanted with Implantable Cardiac Defibrillator (ICD) or those who underwent alcohol septal ablation or surgical septal myomectomy before the first CMR examination.

All studies were performed according to the guidelines of the hospital committee on medical ethics and clinical investigation, and informed consent for the LGE-CMR protocol was obtained from all patients.

LGE-CMR examination:

The cardiac MR examinations were performed on a 1.5 Tesla whole body imaging system (Achieva, Philips Medical System, Best, The Netherlands), using a dedicated cardiac five elements phase-array receiver coil. Balanced steady-state free precession (bSSFP) cine images in the 3 long axis view and in short axis view were used to assess myocardial thickness and to quantify global LV function. Images were acquired during repeated end-expirational breath-old period of 10-15 s. Typical imaging parameters were as follows: field of view 360 to 400 mm, matrix size 256, repetition time [TR] = 3.2 ms, echo time [TE] = 1.3 ms, flip angle = 55 degrees, slice thickness = 8 mm (for both long and short axis view), interslice = 0 (long axis view) and 0.8 mm (short axis view). Subsequently, 15 minutes after intravenous administration of 0.1 mmol/kg gadolinium DOTA (gadolinium-DOTA, Dotarem, Guerbet S.A., Cedex, France) LGE-CMR images were acquired in the same long and short orientations as above described bSSFP images (figure 2). LGE images from long-axial, short-axial, and 4-chamber views were acquired using a breath-hold 3D inversion-recovery turbo-field echo (IR-TFE-3D) sequence (TE: 1.29 ms, TR: 4.4
ms, flip angle: 15 degrees, slide thickness: 7 mm). Inversion times were adjusted to null normal myocardium (230 to 350 ms). LGE images were evaluated using a 17-segment model, as suggested by the American Heart Association criteria [8].

Total acquisition time averaged 40 minutes.

**Images analysis, determination of ventricular and atrial parameters and LGE quantification:**

CMR images were analyzed both qualitatively and quantitatively by two experienced investigators blinded to the electrophysiological findings.

End-diastolic (ED) volumes, end-systolic (ES) volumes, LV stroke volume, ED wall mass, cardiac output and LV ejection fraction were assessed off-line from the images obtained in the short-axis view, using a dedicated commercially available software (ViewForum 3.2, Philips Medical System, Best, The Netherlands). Volume and mass have been measured from short axis images using Simpson's method [9]. All volumes and mass measurements were indexed to body surface area.

The LGE was determined automatically on all short-axis slices using the same dedicated software as above described. A threshold # 6 SD exceeding the mean signal intensity of a non-enhanced myocardial area was used to define areas of LGE (figure 3). Total volume of LGE (measured in grams) was calculated by summing the planimetered areas of LGE in all short axis slices and was expressed as a proportion of the total LV mass (LGE% / total myocardial mass).

LV was evaluated in the short-axis images and divided into equal three circular sections which are basal, mid-cavity and apical segments. Basal and mid cavities were divided into 6 equal segments: basal and mid anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. Apical segments were divided into 4 segments: apical anterior, septal, inferior, and lateral. Apical cap constituted the 17th segment of LV myocardium.

Using the 17-segment model we visually attributed every LGE area at the appropriate segment (figure 4). Each short axis slice was divided into segments obtaining a total of 17 LV segments [8].

**Follow up:**

During a mean follow-up of 40.2±11.1 months, in order to determine the impact of CMR-LGE on prognosis, patients were clinically followed every 12 months by means of physical examination, echocardiography and 24 h-ECG Holter monitoring to evaluate occurrence of arrhythmias. Every arrhythmic events occurred during follow-up were recorded by interviewing with patients, their cardiologists and family physicians. Only new events from
the time of recruitment were considered in the primary or secondary outcomes. Sustained or non-sustained VT were identified by three or more consecutive ventricular beats at a rate (120 beats/ min) and defined as sustained when the duration exceeded 30 s.

**Statiscal analysis:**

All continuous data are expressed as a mean ± standard deviation. Continuous variables were compared with Student's T test or with Mann Whitney test; categorical variables were compared with Chi-square test. The correlation between the location of LGE and the occurrence of VT (NSVT and SVT) is defined as statistically significant if P-value < 0.05.
<table>
<thead>
<tr>
<th>Demographics and Clinical parameters</th>
<th></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 parameters of the study population

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Fig. 2: b-TFE and IR-TFE sequence in short axis view of a patient with HCM.

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Fig. 3: LGE quantification on images acquired by using IR3D sequence and applying the automatic method (6SD).

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Fig. 4: Left ventricle 17-segment model.

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Results

The functional cardiac parameters obtained on LGE-CMR examination in the study population are collected in figure 5. On LGE-CMR, 72 (80%) patients exhibited myocardial scar. The mean LGE extension was 8.11±6.63% of IEDLV mass.

Of 72 patients, LGE involved segment 9 (mid-inferoseptal) in 51 (70.8%) patients, segment 2 (basal-anteroseptal) in 44 (61.1%), segment 8 (mid-anteroseptal) in 38 (52.8%), segment 3 (basal-inferoseptal) in 25 (34.7%), segment 14 (apical-septal) in 22 (30.5%) (figure 6). The remaining segments were involved in less than 30% of cases (figure 7).

During the follow-up period 18 (20%) NSVT and 10 (11.1%) SVT were recorded.

The frequency of LGE involvement for each segment (distinguishing between patients without VT, patients who presented NSVT and those who presented SVT during the follow-up) is explained in graphic 7.

The most frequent segments interested by LGE in patients with NSVT and SVT were segment 2 (respectively 8 patients with NSVT and 5 with SVT), segment 3 (5 NSVT and 2 SVT), segment 8 (12 NSVT and 5 SVT), segment 9 (8 NSVT and 6 SVT) and segment 14 (6 NSVT and 3 SVT). The percentage of subjects presenting with arrhythmic events (NSVT and SVT) with corresponding LGE location is shown in figure 8.

No significant relationship was found between mid-inferoseptal, basal-anteroseptal, basal-inferoseptal and apical-septal location (segments 2, 3, 9 and 14) of LGE and the occurrence of VT. Instead we found a significant correlation between mid-anteroseptal location (segment 8) and the risk of VT (P-value=0.001), as it's showed in graphic 9.
**Fig. 5:** LGE-CMR parameters of the study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 patients</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>64.5 ± 9.8</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>50.6 ± 11.1</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.1 ± 1.6</td>
</tr>
<tr>
<td>ED volume index (ml/m²)</td>
<td>78.8 ± 20.5</td>
</tr>
<tr>
<td>ES volume index (ml/m³)</td>
<td>29.4 ± 17.3</td>
</tr>
<tr>
<td>ED wall mass index (g/m²)</td>
<td>89.5 ± 28.4</td>
</tr>
<tr>
<td>Septal Wall Thickness (mm)</td>
<td>20.5 ± 4.4</td>
</tr>
<tr>
<td>LGE (% of IEDLV)</td>
<td>8.1 ± 6.6</td>
</tr>
</tbody>
</table>

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**Fig. 6:** Patient with HCM who presented a LGE involvement of the segment 8 and 9 on LGE-CMR examination.

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**Fig. 7:** Graphic showing the relationship between the presence of LGE in each LV segment and sustained or non-sustained ventricular tachyarrhythmia (SVT and NSVT) or the absence of ventricular tachyarrhythmia (w/o VT).
**Fig. 8:** Graphic which explain the frequency distribution of arrhythmic events (SVT and NSVT) for each segment interested by LGE.

**Fig. 9:** Graphic that explain the percentage of LGE presence for each segment in patients with and without VT.
Conclusion

LGE most frequently involves the basal and middle third of the ventricular wall, at anterior and inferior junctions between left and right ventricles.

Presence and location of LGE may predict the occurrence of ventricular tachyarrhythmias in HCM patients.

The enhancement involvement of mid-anteroseptal segment is associated with mayor risk of arrhythmic events (VT). Thus LGE detection and localization on LGE-CMR may have a predictive value to stratify HCM patients on arrhythmic risk.
References


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