Patterns of Left Ventricular Hypertrophy and Late Gadolinium Enhancement on Cardiac Magnetic Resonance in Patients with Hypertrophic Cardiomyopathy


Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To evaluate the patterns of left ventricular hypertrophy (LVH) and late gadolinium enhancement (LGE) in hypertrophic cardiomyopathy.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Tertiary Cardiac Care Center, Rawalpindi Pakistan, from Jun 2020 to Dec 2021.

Methodology: Patients having LV hypertrophy due to aortic stenosis, hypertension, athlete’s heart, and infiltrative disorders were excluded from study. Cases were included using nonprobability consecutive sampling. Sample size estimated by taking 0.2-0.5% (1 in 200-500) prevalence of hypertrophic cardiomyopathy using open epi sample size calculator was (n=38) taking 99.99% confidence interval. For the purpose of study all patients with confirmed HCM undergoing CMR during given period were included in study.

Approval from the ethical review committee with IERB (IERB letter # 9/2/R&D/2022/179) was sought. CMR was performed using MRI 3 Tesla. Data analysis was done on SPSS version-26. Quantitative variables were expressed as Mean±SD. Qualitative variables were expressed as frequencies and percentages. ANOVA and student t-test (95% CI and 5% margin of error) was applied to compare the study variables. p-value <0.05 was considered statistically significant.

Results: Majority 77(86.7)% of patients were males. Most common pattern of involvement for LV hypertrophy was asymmetrical septal hypertrophy in 47 (52.8%) followed by apical HCM in 29(32.6%). LVOT obstruction was observed in 3(33.7%) of patients. Mean maximum LV wall thickness was 22mm±5.47mm.

Conclusion: Our study shows association, between the extent of Late Gadolinium Enhancement and LV wall thickness, myocardial mass index in HCM patients. Asymmetrical septal hypertrophy predominantly base to mid septal involvement was documented as most common pattern of hypertrophy.

Keywords: Cardiac magnetic resonance imaging, Hypertrophic cardiomyopathy, Late gadolinium enhancement.


INTRODUCTION

Hypertrophic Cardiomyopathy (HCM) is the most common genetic cardiac disease with autosomal dominant mode of inheritance and is main attributor of sudden cardiac death (SCD) in young.1 It is characterized by defects in sarcomere genes with more than 1400 mutations.2 Disarray and hypertrophy of myocardial myofibirls cause fibrosis predisposing to sudden cardiac death and entails need for vigorous workup including CMR analysis for risk stratification.3

Cardiovascular magnetic resonance (CMR) is sensitive and specific diagnostic tool of HCM cases otherwise unclear by echocardiography.4,5 CMR elaborates morphologic features of different phenotypes and delineates degree and pattern of interstitial and replacement fibrosis accompanying HCM. Late gadolinium enhancement as a symbol of replacement fibrosis on CMR is reported from 60% to 70 % in HCM.6,7 LV wall thickness exceeding 30mm or extensive late gadolinium enhancement involving more than 15% of myocardial mass are high risk CMR features and envisages need for placement of internal cardiac defibrillators.7 The given study is a significant step to highlight the significance of CMR in presenting pattern of left ventricular hypertrophy and late Gadolinium enhancement. Numerous phenotypic features of hypertrophy were also investigated.

Our study was aimed to show association between the Gadolinium Enhancement and various phenotypic features in Hypertrophic cardiomyopathy patients as little data was available on our population.

METHODOLOGY

The analytical cross-sectional study was conducted from June 2020 to December 2021 retrospectively.
Patterns of Left Ventricular Hypertrophy

For the purpose of study hypertrophic cardiomyopathy was diagnosed as greatest thickness within Left Ventricular myocardium having maximal end-diastolic wall thickness of greater than 15mm with cardiovascular magnetic resonance (CMR),8 in absence of another possible cause of hypertrophy. Subtle hypertrophy of 13–14 mm was considered diagnostic in family members of confirmed HCM patients.8

**Sample Size:** It was estimated by taking 0.2-0.5% (1 in 200-500) prevalence of HCM in general population,8 using open epi sample size calculator yielding sample size of (n=38) with 99.99% confidence interval. However, for the purpose of study, all patients with confirmed radiological diagnosis of HCM undergoing CMR during given period were included with sample size of (n=89).

**Inclusion Criteria:** All patients at Tertiary cardiac care center in Rawalpindi, with confirmed diagnosis of Hypertrophic cardiomyopathy (HCM) on cardiac Magnetic resonance imaging (CMR) between June 2020 to December 2021.

**Exclusion Criteria:** Patients with hypertension, athlete’s heart, aortic stenosis and cardiac infiltrative disorders including sarcoidosis and amyloidosis and other causes of left ventricular hypertrophy (LVH) were excluded from study.

Cases were enrolled by nonprobability consecutive sampling. Study was conducted after approval from ethical review committee with IERB (IERB letter # 9/2/R&D/2022/179). CMR was performed using MRI 3 Tesla. LGE images were taken 8–10 min after gadolinium administration. Images were analyzed using Syngo via MR Cardiac Analysis software.

Data analysis was done on SPSS-26. Quantitative variables were expressed as mean and standard deviations. Qualitative variables were expressed as percentages and frequencies. Data was further subdivided based on phenotypes and pattern of late gadolinium enhancement. Qualitative data were compared using the Chi square test. Continuous data were compared using ANOVA test and independent samples t-test. p<0.05 was considered statistically significant.

**RESULTS**

Mean age of presentation was 45.6±14 years. Majority 77(86.7%) cases were males. Most common pattern of LVH was asymmetrical septal hypertrophy in 47(52.8%) followed by apical HCM in 29(32.6%). Left ventricular outflow tract (LVOT) obstruction was observed in 30(33.7%) patients (Table-I).

| Table-I: Clinical Parameters and Phenotypic Characteristics of Morphology |
|---------------------------|------------------|
| **Variables**          | **n(%)**          |
| Age (years)         | 45.6±14.03       |
| Gender             | Males:77(86.5%)  |
|                     | Female:12(13.5%) |

**Site and Pattern of Morphology**

- Asymmetrical Septal Hypertrophy(ASH): 47(52.8%)
- ASH With Sigmoid Shape: 26(29.2%)
- ASH With Reverse Curve Counter: 19(21.3%)
- Apical HCM: 29(32.6%)
- Mid Ventricular: 9(10.1%)
- Concentric (Neutral): 6(6.7%)

**Characteristics Of Morphology**

- Resting LVOT Obstruction: 30(33.7%)
- SAM: 36(40.4%)
- Maximum LV Thickness: 22.14 mm
- T1 MYOMAPS: 1314.42 msec
- T2 MYOMAPS: 40.9 msec
- Anterior Mitral Leaflet(AML)Length mm: 23.4mm
- Posterior Mitral Leaflet Length mm: 12.4 mm
- Papillary Muscle Hypertrophy: 13(8.1%)
- Myocardial Crypts: 17.4% (n=15)

**CMR Volumetric Parameters**

- EDV: 137.5 ml
- ESV (ml): 47.05 ml
- EF %: 66.27%
- Stroke Volume: 90.14 ml
- CO: 6.47 l/min
- LV Mass Index: 98.5g/m²
- LAVI: 34.47 ml/m²

*ASH= Asymmetrical Septal Hypertrophy, RC= Reverse Septal Curve, SAM= Systolic Anterior Motion, LAVI= Left Atrial Volume Index, LGE= Late Gadolinium Enhancement

Late gadolinium enhancement was observed in 76(85.4%) (Figure-1).

![Figure-1: Pattern of Late Gadolinium Enhancement](image)

Most common pattern was diffuse patchy involvement 64(71.9%) with predominant involvement of antero-septal wall in 67(75.3%) cases.

Pattern and extent of LGE was associated with LV wall thickness (p=0.01), myocardial mass index (p=...
-0.025), cavity obstruction (p=0.026) and increased LAVI (p=0.05) and insignificant reduction in LVEF (p=0.412) (Table-II).

Table-II: Comparison between Characteristics of patients with and without Late Gadolinium Enhancement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Focal</th>
<th>Diffuse</th>
<th>Absent</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(%)</td>
<td>12(33.5)</td>
<td>64(71.9)</td>
<td>13(14.6)</td>
<td>0.051</td>
</tr>
<tr>
<td>LAVI ml/m²</td>
<td>33.5</td>
<td>36.1</td>
<td>27.67</td>
<td></td>
</tr>
<tr>
<td>LVEF %</td>
<td>66.37%</td>
<td>65.58%</td>
<td>69.6%</td>
<td>0.412</td>
</tr>
<tr>
<td>Myocardial Mass Index (g/m²)</td>
<td>76.28</td>
<td>105.99</td>
<td>80.8</td>
<td>0.025</td>
</tr>
<tr>
<td>Maximum LV Wall Thickness (mm)</td>
<td>17.8</td>
<td>23.69</td>
<td>18.73</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cavity Obstruction n (%)</td>
<td>7 (7.7%)</td>
<td>74(82.7%)</td>
<td>8(9.6%)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

LAVI=left atrial volume index; LVEF=left ventricular ejection fraction

Asymmetrical septal hypertrophy with reverse septal curve morphology was present in relatively young individuals. Systolic anterior motion (SAM) and left ventricular outflow tract (LVOT) obstruction were more common in sigmoid phenotypes as compared to reverse curve phenotype (p=0.012) and (p=0.475) respectively, whereas LV mass index (p=0.048), prevalence of LGE (p=0.076) and maximum LV wall thickness (p=0.042) were higher in reverse septal curve morphology as compared to sigmoid morphology. Myocardial crypts were also more common in reverse septal curve morphology in 6(33.3%) as compared to sigmoid morphology (p=0.299). LGE was less common in apical variants as compared to other variants.

Most common pattern of LV hypertrophy was septal in 75(84.3%) patients (Figure-2) predominantly involving Basal to mid-level of LV myocardial in 52(58.4%) patients.

DISCUSSION

HCM commonly presents in adolescence, with 71% male predisposition as documented in NHLBI HCM registry. Mean age of presentation of HCM in our study was 46.5±14 years with majority of patients being males.

Six phenotypes of HCM are documented in NHLBI registry which include isolated basal septal hypertrophy in 46% cases, reverse septal curvature phenotype in 40% of cases, apical phenotype in 9%, mid-cavity obstructive phenotype with apical aneurysm accounting for 3% of cases while concentric HCM in 1%, and miscellaneous in 1%. In our study Asymmetric septal hypertrophy was most common phenotype accounting for 45(52.8%) cases followed by apical HCM in 29(32.6%) cases.

Asymmetric septal hypertrophy (ASH) with sigmoid septal counter is most common variant of HCM. It usually presents in elderly patients with little association with gene mutations. It is commonly associated with systolic anterior motion (SAM) and Left ventricular outflow tract obstruction (LVOT) in up to 30% cases.

Figure-2: Pattern of LV Hypertrophy in HCM

Other characteristics including myocardial crypts were present in 17.4% (15 patients). Papillary muscle hypertrophy was found in 8.1% patients (13 cases). Pericardial effusion was observed in (n=2; 2.2%) of total, both having concentric phenotype (33.3% prevalence within phenotype). AP band was present in 7 patients (7.9%) prevalence). Comparison of ASH characteristics of patients with different Phenotypes are depicted in Table-III.

Table -III: Comparison of ASH characteristics of patients with different Phenotypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>ASH Sig</th>
<th>ASH RC</th>
<th>Apical</th>
<th>Concentric</th>
<th>Mid Cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.7</td>
<td>34.3</td>
<td>49.3</td>
<td>50.8</td>
<td>50.2</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>20 (26%)</td>
<td>18 (23.4%)</td>
<td>27 (35.1%)</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6 (50%)</td>
<td>1 (8.3%)</td>
<td>0 (0%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>LGE presence</td>
<td>22 (84.6%)</td>
<td>19 (100%)</td>
<td>20 (69%)</td>
<td>6 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>LVOT Obstruction</td>
<td>11 (42.3%)</td>
<td>6 (31.6%)</td>
<td>1 (3.4%)</td>
<td>3 (50%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Maximum LV Wall Thickness</td>
<td>21.06</td>
<td>24.8</td>
<td>19.6</td>
<td>26.3</td>
<td>26.25</td>
</tr>
<tr>
<td>LV MASS INDEX g/m²</td>
<td>88.99</td>
<td>113.45</td>
<td>80.66</td>
<td>136.49</td>
<td>124.64</td>
</tr>
<tr>
<td>EF</td>
<td>66.66%</td>
<td>65.37</td>
<td>66.9</td>
<td>70.09</td>
<td>62.48</td>
</tr>
<tr>
<td>SAM</td>
<td>18 (69.2%)</td>
<td>6 (31.6%)</td>
<td>5 (17.2%)</td>
<td>3 (50%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>LAVI ml/m²</td>
<td>37.4</td>
<td>36.4</td>
<td>30.3</td>
<td>30.3</td>
<td>39.5</td>
</tr>
</tbody>
</table>
26(29.2%) cases. LVOT obstruction was present in 11(42.3%) cases and SAM was present in 18(69.2%) cases presenting with sigmoid morphology in our study.

Asymmetric septal hypertrophy with reversed septal phenotype and crescentic LV cavity presents at younger age with less common LVOT obstruction, however it has strong association with genetic mutations in as much as 58-73% cases, accompanied with extensive late gadolinium enhancement. About 93% of patients with reverse septal counter morphology were found to have greater than 15% LGE involvement of LV myocardium in NHLBI registry. ASH with reversed curve morphology was present in 19(21.3%) cases in our study.

Apical HCM with spade like LV cavity or Yamaguchi variant has increased incidence in Asians especially Japanese population ranging from 25% in Japan to less than 2% in west. It affects middle aged men and does not carry bad prognosis. Apical HCM was present in 32% of our study population. This may be accounted by increased prevalence of ECG changes (deep T inversions) in apical HCM p<0.001 warranting extensive workup in this population. LVOT obstruction was present in 3.4% cases whereas apical LV cavity obliteration was observed in as much as 79.3% cases.

Concentric HCM with a small cavity size, has reported incidence as high as 42%. However it only accounted for 6.7% of our study population.

HCM with mid ventricular obstruction is characterized by marked hypertrophy at mid-ventricular level with hour glass or dumbbell appearance of LV cavity. Progression of disease causes LV apical aneurysm or apical clot formation. Mid ventricular variants accounted for 9(10.1%) cases in our study population. Apical aneurysm was present in 2 patients and apical LV thrombus was present in 1 patient with this variant.

Mass like involvement of LV free wall with variable degree of contractility on tagging sequence is rare variant. We did not observe any case with this variant in our study population.

Elongated anterior and posterior mitral leaflets have been reported by CMR in HCM. (26±5 mm versus 19±5 mm, p<0.001 for anterior mitral leaflets, and 14±4 mm versus 10±3 mm, p<0.001 for Posterior Mitral Leaflet incases with LVOT obstruction as compared to cases with no LVOT obstruction respectively and is implicated in obstructive physiology. Mitral leaflets were elongated in our study with mean length of 23.4±3.5mm for anterior mitral leaflet (AML) and mean posterior mitral leaflet (PML) length of 12.5±2.1 mm. AML was 25.09±3.8mm for patients with LVOT obstruction and 23.2±3.2mm in patients without LVOT obstruction. (p-value =0.022). PML was 12.3±2 mm in patients without LVOT obstruction and 12.8±2 mm in patients with LVOT obstruction (p=0.357).

LV mass indexed to BSA is increased in HCM patients. Increased LV mass index was present in 34.4%(55 cases) Mean Myocardial mass index in our study was 98.5±42.8 g/m2 with mean 96.5±39 g/m2 for men and 111.5±62 g/m2 for women. This is contrary to documented myocardial mass index distribution in literature of 104g/m2 in men and 89 g/m2 in women with HCM. This could be accounted for by higher incidence of concentric and mid ventricular phenotypes in female in our study with relatively greater myocardial mass index and higher prevalence of apical variant in males with relatively preserved LV mass index.

Increased Myocardial mass index is associated with increased maximal LV thickness (p<0.001) and LVOT obstruction (p<0.001). Increased LV mass index was associated with significant increase in maximum LV wall thickness (24.1±2.26 mm VS 18.9±2.2 mm in patients with normal LV mass index (p<0.000), increased incidence of resting LVOT obstruction (43.6% cases with increased myocardial mass index vs 18.2% cases with normal myocardial mass index (p-value 0.015), however incidence of LGE was not significantly increased with increased LV mass index (89.1% vs 81.8%: p-value 0.354) in current study. There was significant relation between myocardial mass index and LVOT obstruction in our study. Myocardial mass index was 132±18 g/m2 in cases with LVOT obstruction and 81±18 g/m2 in cases without LVOT obstruction( p<0.000) in our study.

Left atrial volume index(LAVI) is increased in patients with asymmetrical septal hypertrophy (ASH) and is associated with increased incidence of atrial fibrillation (AF) and heart failure. LAVI was greater in patients with Asymmetrical and mid ventricular phenotypes as compared to cases with concentric and apical variants (p=0.073).

Extensive LGE is associated with increased risk of sudden cardiac death (p<0.001), with longer runs of NSVT (p=0.02). Study Carried out in Pakistan at Agha Khan between 2011-2019 depicted higher prevalence of
Patterns of Left Ventricular Hypertrophy

LGE i.e. 56 cases (75.7%) as compared to previously reported LGE of 60% in literature.\(^1,18\) There was frequent septal and free left ventricular wall involvement (24.3%, n =18).\(^19\) Other studies have documented the incidence of LGE in HCM of 84% and 80% respectively with majority (89%) patients showing patchy and mid wall involvement.\(^11,19\) LGE was reported in 76(85.4%) cases in our study. With predominant involvement of antero-septal wall 67(75.3%) with base to mid distribution 29(35.6%) cases.

Extent of Late gadolinium enhancement is directly related to presence of male gender (\(p=0.007\)), maximum thickness of LV myocardium (\(p=0.006\)) and LV mass index (\(p=0.031\)).\(^20\) Study by Maron showed that patients with LGE had maximal LV wall thickness of 23mm and LV mass index of 113g/m\(^2\) as compared to patients lacking gadolinium enhancement (20mm, 100g/m\(^2\)); \(p=0.001\) and \(p=0.02\), respectively these patients also had lower EF.\(^21\) In our study LGE was associated with increased LV wall thickness (\(p=0.014\)), increased LAVI (\(p=0.02\)). LV mass index was increased in patients with extensive LGE (\(p=0.025\)) and there was increased incidence of LVOT obstruction in patients with LGE (\(p=0.032\)).

T1 myomaps representing diffuse interstitial fibrosis are prolonged in patients with HCM.\(^22\) High T2 signal are found in early course of disease and represent progression of myocardial fibrosis originating as acute inflammation with high T2 signal, and culminating in chronic fibrosis with T2 signal normalization.\(^23\) In our study T1 times were increased (1314.42 msec) whereas T2 times were within normal limits (40.9msec) consistent with presence of delayed interstitial fibrosis in these cases. The prevalence of apico basal bundle in literature is reported to be much higher with 63% to 69% prevalence in HCM and 60% genotype positive patients as compared to 10% in general population.\(^24\) Apico basal bands were present in small percentage in our study population.

LIMITATIONS OF STUDY

The study was retrospective cross sectional study and results can be influenced by recall bias. More detailed prospective studies with larger sample size needed in future to cover all aspects in more detail.

CONCLUSION

Most common pattern of LVH in our study was asymmetrical septal hypertrophy involving basal to mid septum, followed by apical HCM. There was significant variation of characteristics between different phenotypes. SAM and LVOT obstruction were more common in sigmoid morphology as compared with reverse septal curve morphology. Whereas Reverse septal morphology was associated with younger age at presentation, increased LV mass index, increased LV wall thickness and presence of myocardial crypts when compared with sigmoid morphology. LV mass index, anterior and posterior mitral leaflet lengths were significantly increased as compared to general population.

Late gadolinium enhancement was observed in majority of cases. Most common pattern of LGE involvement was diffuse patchy involvement of basal antero-septal wall. Presence and extent of LGE was associated with increased maximal LV wall thickness, LV mass index, LVOT obstruction and increased LAVI with insignificant reduction in LVEF.

ACKNOWLEDGEMENT

I am deeply grateful to my supervisor for his guidance, patience and support who provided insight and expertise that greatly assisted my research project. I also want to share my gratitude for Comdt Exec Dir AFIC/NHID & HoD R&D for their support and contribution in completion of the research paper.

Conflict of Interest: None.

Author Contribution

Following authors have made substantial contributions to the manuscript as under:

SM: Concept, study design, drafting the manuscript
AA: Concept, study design, drafting the manuscript
AHS: Concept, study design, drafting the manuscript
ARJ: Concept, study design, drafting the manuscript
GRM: Concept, study design, drafting the manuscript
SAS: Data collection, data analysis
JK: Analysis, manuscript writing and proof reading
NS: Data collection, data analysis and review of article
W: Manuscript writing, concept and editing
IKA: Data collection, data analysis and review of article

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

15. Olivotto I, Maron M. Assessment and significance of left ventricular mass by Cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008; 52(7): 559-566.