PROJECT REPORT

Submitted during the course of

DM Cardiology

Dr. HARIKRISHNAN.G
DM Trainee

DEPARTMENT OF CARDIOLOGY

Jan 2011 – Dec 2013
DECLARATION

I, Dr. Harikrishnan.G, hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram  
Date  
Dr Harikrishnan.G  
DM Trainee

Forwarded

The candidate, Dr Harikrishnan.G, has carried out the minimum required project.

Thiruvananthapuram  
Date  
Prof. Dr Thomas Titus  
Head of Department of Cardiology
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ROLE OF cMRI IN RISK ASSESSMENT OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY
Introduction
INTRODUCTION

Hypertrophic cardiomyopathy is a heterogeneous condition characterized by varied clinical course and outcome. Many patients have little or no discernible cardiovascular symptoms, whereas others have profound exercise limitation and recurrent arrhythmias. Of the various clinical manifestations sudden cardiac death (SCD) is the most worrisome in that most of the affected individuals are relatively asymptomatic young adults and SCD may be the first manifestation of this disease. SCD in hypertrophic cardiomyopathy is considered to be related to ventricular tachycardias. The only intervention known to be effective in prevention of SCD is insertion of an implantable cardioverter defibrillator; with antiarrhythmic drugs having questionable efficacy if at all useful. While the decision to implant an ICD in a patient who has survived a cardiac arrest is straightforward, its role in a patient with hypertrophic cardiomyopathy as a primary preventive strategy is still being debated. Since insertion of an ICD is an invasive procedure and its appropriateness in a particular patient needs to be assessed, clinicians
are ever in search of better methods to risk stratify patients with hypertrophic cardiomyopathy. The classical risk markers defined for SCD in hypertrophic cardiomyopathy in a patient who has not yet suffered a cardiac arrest include unexplained syncope, repetitive nonsustained ventricular tachycardia (NSVT), severe left ventricular wall thickening, family history of SCD and abnormal blood pressure response to exercise, with presence of Atrial fibrillation, LV outflow tract obstruction, myocardial bridging, high risk genetic mutations etc. But even a combination of 2 or more of classical risk factors in a patient is known to predict the occurrence of Ventricular tachycardia or ventricular fibrillation in only about 23% over medium term follow up.

The development of cMRI techniques for detection of myocardial fibrosis by Late gadolinium enhancement has opened up the possibility of improving risk stratification in patients with hypertrophic cardiomyopathy, with the logical assumption that the areas of myocardial fibrosis acts as nidus for occurrence of ventricular tachyarrhythmias. This has been studied in western population and it has been shown that LGE correlates well with occurrence of ventricular
Introduction

tachyarrhythmias and shows a trend towards increased incidence of SCD and appropriate ICD discharges. To our knowledge, such data in an Indian cohort has not been generated yet.
Hypothesis
HYPOTHESIS

LGE detected by cMRI is associated with increased incidence of ventricular arrhythmias in patients with hypertrophic cardiomyopathy.
Objectives
OBJECTIVES

To correlate LGE in cMRI with occurrence of ventricular arrhythmias in patients with Hypertrophic cardiomyopathy.

To assess the association of ventricular arrhythmias with the extent of LGE in cMRI in patients with hypertrophic cardiomyopathy.

To describe the pattern of LGE in an Indian population with hypertrophic cardiomyopathy.

To assess the correlation between segmental wall thickness described by cMRI and presence of ventricular arrhythmias in patients with hypertrophic cardiomyopathy.
Review of Literature
Hypertrophic cardiomyopathy has been defined as “a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient, with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy.” Clinically, HCM is usually recognized by maximal LV wall thickness $\geq 15$ mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information (e.g., family history of HCM), based on echocardiography. In the case of children, increased LV wall thickness is defined as wall thickness $\geq 2$ standard deviations above the mean ($z$ score $\geq 2$) for age, sex, or body size.\(^1\) HCM is a heterogeneous cardiac disease with a diverse clinical presentation and course, presenting in all age groups from infancy to the very elderly. While majority has normal life expectancy, 3 different, but not mutually exclusive pathways of progression has been described for this entity.
(i) SCD due to unpredictable ventricular tachyarrhythmias, most commonly in young asymptomatic patients $\leq 35$ years of age.

(ii) Heart failure that may be progressive despite preserved systolic function and sinus rhythm, or in a small proportion of patients, heart failure may progress to the end stage with LV remodeling and systolic dysfunction caused by extensive myocardial scarring.

(iii) AF, either paroxysmal or chronic, also associated with various degrees of heart failure and an increased risk of systemic thromboembolism and both fatal and nonfatal stroke.

While only a minority of HCM patients ($1\%$ per year)\(^2\) are at risk for SCD, it is also the most devastating complication as it occurs in young population and at times may be the first indication of any cardiac illness. Most of these SCDs are known to be of arrhythmic origin (ventricular arrhythmias). ICDs offer the only effective means of preventing SCD and prolonging life in patients with HCM.\(^2\) Selection of patients who are appropriate for implantation for primary as opposed to secondary prevention can be a difficult clinical decision, owing to the individuality of each patient and family, variable definitions for risk markers, sparse clinical data, the relative infrequency of both HCM and
SCD in most clinical practices, and the cumulative morbidity of living with an ICD.

The risk factors considered to be predictive of high risk for subsequent SCD include

(i) Prior Personal History of Ventricular Fibrillation, SCD, or Sustained VT: - The annualized rate of subsequent events is approximately 10% per year, although it has been shown that individuals may have no recurrent events or may have decades-long arrhythmia free intervals between episodes.3,4

(ii) Family History of SCD: - Some studies have used a definition of SCD in >/=2 first-degree relatives 5, whereas others have counted a single event.6

(iii) Syncope: - syncope that was unexplained or thought to be consistent with arrhythmia (i.e., not neurally mediated) showed a significant independent association with SCD only when the events occurred in the recent past (<6 months) but not if the syncopal episodes occurred >/= 5 years before the clinical visit7
(iv) Nonsustained Ventricular Tachycardia: - Intuitively, it would seem appropriate to place more weight on frequent, longer, and/or faster episodes of NSVT; however, there have been no systematic investigations of whether number of episodes and duration or ventricular rate of episodes of NSVT definitely have an impact on SCD risk.¹

(v) Maximum LV Wall Thickness: - when magnitude of hypertrophy is ≥30 mm, there is an independent association with SCD ⁸

(vi) Abnormal Blood Pressure response during exercise: - For up to a third of patients with HCM, there is an inappropriate systemic systolic blood pressure response during exercise testing (defined as either a failure to increase by at least 20 mm Hg or a drop of at least 20 mm Hg during effort). It has been postulated that this finding is a risk factor for SCD.⁹

However none of these risk factors are 100% sensitive or specific for prediction of SCD and need for ICD. The presence of two or more risk factors had a positive predictive accuracy of 23% and a negative predictive accuracy of 90% for SCD during (medium term) follow up.⁵ It is in this context that the search for newer risk prediction tools brought
forward late gadolinium enhancement in cMRI as a predictor of ventricular arrhythmias. Because LGE is believed to represent myocardial fibrosis or scarring, it has been hypothesized that LGE may represent myocardium prone to ventricular tachyarrhythmia. 10

Gadolinium-DTPA diffuses rapidly out of capillaries (unlike echocardiographic microbubbles), into tissue but cannot cross intact cell membranes. So after an intravenous bolus, both normal and abnormal myocardium passively accumulates Gd-DTPA, but with time, because of slower kinetics, and a larger volume of distribution, abnormal myocardium possesses a slightly larger amount per unit volume of Gd-DTPA. Gadolinium contrast is used in concert with an MRI technique called inversion-recovery. This technique is highly sensitive to subtle regional differences in gadolinium concentration, and is an “image intensification” technique. The consequence is an “all-or-none” technique with very high sensitivity to regional interstitial expansion, and heterogeneity, but with little information about the actual extent of the interstitial compartment in either the nulled (dark), or enhancing (bright) myocardium. All that is known is that they are on different sides of a threshold.
In patients with HCM, there may be a generalized increase in the normal interstitium with pericellular, intercellular, and fascicular connective tissue. In extreme cases, individual myocytes may become encased in collagen. Myofibre disarray is also, but not ubiquitously associated with fibrosis, called plexiform fibrosis. Other types of fibrosis in HCM are perivascular fibrosis and microscopic replacement scars. Fibrosis in HCM can occur throughout the myocardial wall, even with subendocardial sparing. In addition, areas of focal myocardial disarray and fine interstitial fibrosis may be seen. Delayed enhancement is thought to occur in areas of abnormal myocardium secondary to expansion of the extracellular space, alterations in the extracellular matrix composition, and altered distribution kinetics. Therefore, the distribution and pattern of gadolinium uptake will be different between these two conditions. The different patterns of hyperenhancement seen are likely to be linked to the different pathologic processes occurring in different patients, and the different stages that such processes had reached at the time of scanning. However it has been suggested that areas of visually detected delayed enhancement are most likely explained by macroscopic replacement fibrosis and that enhancement secondary to diffuse interstitial processes, such as plexiform fibrosis, is less likely to
cause recognizable differences in regional signal intensity.\textsuperscript{15} Delayed enhancement occurs in up to 80\% of patients with HCM. The most common form of hyperenhancement in HCM is patchy and mid wall in location.\textsuperscript{10,16}

Various studies have found that an increased percentage of histologic collagen correlated directly with increased delayed enhancement of the myocardium. It is also shown that increased enhancement was associated with an increased incidence of regional wall motion abnormalities.\textsuperscript{17,18} Delayed enhancement tends to involve the interventricular septum, particularly the anteroseptal mid to basal segments. These segments are also the most commonly thickened segments in patients with asymmetric HCM. If abnormal enhancement occurs elsewhere outside the interventricular septum, it also tends to occur in areas of maximal left ventricular thickness. Another interesting feature of delayed enhancement in HCM is a predilection for enhancement to occur at the anterior and posterior right ventricular insertion points. An exception to this is in areas of burned out myocardium where the left ventricular wall is typically thinned and enhancement is full thickness.\textsuperscript{18,19,20}
As myocardial fibrosis may provide the underlying arrhythmogenic substrate in HCM, there has been significant interest in determining whether late gadolinium enhancement (LGE) by CMR is an independent risk factor for predicting SCD and other adverse outcomes. It has been shown that there is greater extent of LGE in patients with progressive disease. It was also demonstrated that the extent of LGE is more in patients with 2 or more classical risk factors for SCD. The authors also found that there was increased discrimination for risk factors for SCD in younger population (<\= 40 years). Patients with diffuse rather than confluent enhancement had >\= 2 risk factors for sudden death. LGE was found to be associated with increased prevalence of Premature ventricular contractions (PVCs), couplets, and nonsustained ventricular tachycardia (NSVT). LGE was found to be an independent predictor of NSVT (relative risk 7.3, 95% confidence interval 2.6 to 20.4; p < 0.0001). In patients with symptomatic apical hypertrophic cardiomyopathy also similar results have been reproduced with the patients with ventricular arrhythmias having greater numbers of hyperenhanced myocardial segments (P< 0.01) and larger percentages of hyperenhanced myocardial mass (P< 0.05) in the LV apex.
Hard clinical endpoints also correlated with the extent of fibrosis detected by LGE in CMR. In a cohort of 217 patients followed up for more than 3 years, 25% in the fibrosis group but only 7.4% patients without fibrosis reached the combined primary end point of cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia or ventricular fibrillation, or appropriate implantable cardioverter-defibrillator discharge (hazard ratio [HR]: 3.4, p = 0.006). The extent of fibrosis and nonsustained ventricular tachycardia were univariate predictors for arrhythmic end points (sustained ventricular tachycardia or ventricular fibrillation, appropriate implantable cardioverter-defibrillator discharge, sudden cardiac death) (HR: 1.30, p _ 0.014). Nonsustained ventricular tachycardia remained an independent predictor of arrhythmic end points after multivariate analysis, but the extent of fibrosis did not.23 The presence of any LGE yielded an odds ratio for death of 5.47 in the all-cause mortality and 8.01 in the cardiac mortality group. The authors also suggested that LGE may be a better predictor of all cause and cardiac mortality compared to classical risk factors, because in their data set the presence of 2 risk factors yields an odds ratio of 3.86 for all-cause and of 2.20 for cardiac mortality, respectively. Presence of LGE also predicted SCD with an odds ratio of 5.14, though not reaching statistical
Review of Literature

significance because of the low number of events in the population. The estimated six year SCD-free survival rates according to the number of risk factors present were as follows: 0 (n = 203), 95% (CI 91% to 99%); 1 (n = 122), 93% (CI 87% to 99%); 2 (n = 36), 82% (CI 67% to 96%); 3 (n = 7), 36% (CI 0% to 75%). In another study which followed up 424 HCM patients for 3.6 years, LGE-positive patients were more likely to have episodes of nonsustained ventricular tachycardia (34 of 126 [27%] versus 8 of 94 [8.5%], P<0.001), had more episodes of nonsustained ventricular tachycardia per patient (4.5+/−12 versus 1.1+/−0.3, P=0.04), and had higher frequency of ventricular extrasystoles/24 hours (700+/−2080 versus 103+/−460, P=0.003). Of the 4 patients who suffered SCD or appropriate ICD discharges all were LGE positive yielding an event rate of 0.94%/y, P<0.01 versus LGE negative. Univariate associates of SCD or appropriate ICD discharge were positive LGE (P=0.002) and presence of nonsustained ventricular tachycardia (P=0.04).

Over the past decade multiple studies have demonstrated the utility of myocardial fibrosis picked up by LGE in CMR as an independent predictor of adverse cardiovascular outcomes including ventricular arrhythmias and SCD. This association, in some studies, had a more robust predictive value compared to traditional risk factors. ACCF/AHA
Hypertrophic Cardiomyopathy Guideline 2011 gives a Class IIb recommendation for using cardiac magnetic resonance imaging when SCD risk stratification is inconclusive after documentation of the conventional risk factors. So CMR imaging with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision making.¹
Materials & Methods
MATERIALS AND METHODS

The present study was done in the Department of Cardiology in coordination with Department of Radiology in a tertiary care referral centre in South Kerala (SCTIMST, Trivandrum). It was done as an observational study in patients attending Cardiology OPD who had a diagnosis of hypertrophic cardiomyopathy. It was done from 1st of July 2011 to 31st of December 2013.

INCLUSION CRITERIA

All patients with a diagnosis of hypertrophic cardiomyopathy after the initial clinical, 12 lead electrocardiographic and transthoracic echocardiographic evaluation, attending Department of Cardiology Outpatient department, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

EXCLUSION CRITERIA

Patients with coronary artery disease - documented myocardial infarction at any time in the past, more than 50% stenosis in epicardial coronary arteries by coronary angiogram.
Patients who are unable to undergo cMRI due to any reason like implanted ICD, nonMRI compatible prosthesis, claustrophobia

Patients with renal dysfunction – serum Creatinine more than 1.4mg/dl

Patients not willing to undergo cMRI

PROTOCOL

All patients who are diagnosed to have hypertrophic cardiomyopathy after initial evaluation in OPD (including history, physical examination, ECG and Echocardiography) were screened for enrollment into the study. Those satisfying inclusion and exclusion criteria were explained the details of the study and a detailed consent was taken. In addition to the initial evaluation, these patients underwent a 24 hour ambulatory ECG monitoring and cMRI. 24 hour ambulatory ECG recording was evaluated for presence of sustained or nonsustained ventricular tachycardias. Nonsustained ventricular tachycardia was defined as presence of more than or equal to 3 consecutive ventricular complexes occurring at a rate of more than or equal to 100 beats per minute and lasting for less than 30 seconds. Such rhythm lasting for
Materials and Methods

more than 30 seconds was termed sustained ventricular tachycardia. The presence of other rhythm abnormalities including supraventricular tachyarrhythmias, bigeminal rhythm, bradyarrhythmias and total VPC load was also documented. cMRI was done with a 1.5 Tesla Avento Siemens machine. Late gadolinium Enhancement was documented at 20 minutes after intravenous bolus infusion of 0.1mmol/kg of Gadolinium from Phase Sensitive Inversion Recovery (PSIR) sequences. Late gadolinium enhancement and segmental wall thickness was documented the standard 17 segment model for LV.
The presence of mitral regurgitation, systolic anterior motion of mitral valve, and left and right ventricular function was also documented. MRI report was validated by an experienced physician who was blinded to the clinical details and 24 hour ambulatory ECG recording data. Patients in whom coronary artery disease was suspected or LV outflow tract obstruction needed to be quantified prior to intervention and those undergoing ICD implantation were also subjected to coronary angiogram and detailed catheterization studies. Those found to have significant epicardial coronary artery disease (more than 50% diameter stenosis) were excluded from final analysis.

Data including age, sex, clinical features, family history of SCD, echocardiographic wall thickness, LVOTO by echo (and cardiac catheterization if available), segmental wall thickness and LGE by cMRI in the 17 segmental model, 24 hour ambulatory ECG recording data was compiled and analyzed by SPSS software version 18. Pearson t test and Chi square test was used for analysis as applicable.
Results
RESULTS

Of the 80 patients screened for the study, 57 patients were available for final analysis.

Eleven patients were excluded because of associated Coronary artery disease or contraindications to cMRI. MRI could not be undertaken in 4 patients because of claustrophobia and in 3 patients due to renal dysfunction. Among these 62 patients who underwent cMRI 3 had coronary artery disease in coronary angiography and 2 did not have evidence of HCM by cMRI.
Males constituted 73.7% (42 of 57 patients) of study population. Mean age was 42.3 ± 18.4 years.

Twenty seven patients had obstructive HCM (Peak Gradient >30mm) and 5 patients had apical HCM.

Mean follow up period was 12.5±3.98 months.

Dyspnoea was the most common presenting symptom present in 59.6% of patients. 17.5% of patients were totally asymptomatic. (Fig1)

![Presenting Characteristics](image)

**Figure 1**
### Results

<table>
<thead>
<tr>
<th></th>
<th>Ventricular arrhythmias present (%)</th>
<th>Ventricular arrhythmias absent (%)</th>
<th>Total (%)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
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<td><strong>Sex</strong></td>
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<td>10 (23.8)</td>
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<td>8 (19)</td>
<td>13 (22.8)</td>
<td>1.28</td>
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<tr>
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<td>44 (77.2)</td>
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<td>12 (28.6)</td>
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<td>9 (21.4)</td>
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<tr>
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<td>8 (53.3)</td>
<td>33 (78.6)</td>
<td>41 (71.9)</td>
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</table>

**Table 1**

Ventricular arrhythmias were present in 26.3% of total population of which 10.5% had sustained ventricular arrhythmias. The sex distribution and presentation was similar in groups with and without ventricular arrhythmias. (Table 1)
Late Gadolinium Enhancement (LGE) was present in 25 of 57 (43.9%) patients. Most common pattern of enhancement was in the mid myocardial region. (Fig 2)
Results

Baseline                           Midmyocardial pattern of LGE

Transmural pattern of LGE           Subendocardial pattern of LGE
The sex distribution and presentation was similar in groups with and without LGE. (Table 2)

<table>
<thead>
<tr>
<th></th>
<th>LGE present (%)</th>
<th>LGE absent (%)</th>
<th>Total (%)</th>
<th>$\chi^2$</th>
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<td>20(80.0)</td>
<td>22(68.8)</td>
<td>42(73.7)</td>
<td>0.52</td>
<td>0.47</td>
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<tr>
<td>Female</td>
<td>5 (20.0)</td>
<td>10(31.3)</td>
<td>15(26.3)</td>
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<tr>
<td><strong>Asymptomatic</strong></td>
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<tr>
<td>Positive</td>
<td>5 (20.0)</td>
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<td>10(17.5)</td>
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<td>20(80.0)</td>
<td>27(84.4)</td>
<td>47(82.5)</td>
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<tr>
<td><strong>Presyncope</strong></td>
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<td>Positive</td>
<td>9 (36.0)</td>
<td>8 (25.0)</td>
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<td><strong>Syncope</strong></td>
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<td>9 (36.0)</td>
<td>4 (12.5)</td>
<td>13(22.8)</td>
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<tr>
<td>Negative</td>
<td>16(64.0)</td>
<td>28(87.5)</td>
<td>44(77.2)</td>
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<tr>
<td><strong>Dyspnoea</strong></td>
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<tr>
<td>Positive</td>
<td>14(56.0)</td>
<td>20 (62.5)</td>
<td>34(59.6)</td>
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<td>0.56</td>
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<td>Negative</td>
<td>11(44.0)</td>
<td>12(37.5)</td>
<td>23(40.4)</td>
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<tr>
<td><strong>Chestpain</strong></td>
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<td>4 (16.0)</td>
<td>11(34.4)</td>
<td>15(26.3)</td>
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<td>Negative</td>
<td>21(84.0)</td>
<td>21(65.6)</td>
<td>42(73.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Palpitations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>12(48.0)</td>
<td>9 (28.1)</td>
<td>21(36.8)</td>
<td>2.38</td>
<td>0.12</td>
</tr>
<tr>
<td>Negative</td>
<td>13(52.0)</td>
<td>23(71.9)</td>
<td>36(63.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family history of SCD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>10(40.0)</td>
<td>6 (18.8)</td>
<td>16(28.1)</td>
<td>3.49</td>
<td>0.06</td>
</tr>
<tr>
<td>Negative</td>
<td>15(60.0)</td>
<td>26(81.3)</td>
<td>41(71.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Mean age of patients with ventricular arrhythmias was 43.4 ± 17.4 years Vs 42 ± 19 years in those without ventricular arrhythmias (p=0.797). The mean age of patients with LGE was 39.9 ± 17.4 years Vs 44.2 ± 19.3 years in patients without LGE. But this was not statistically significant (p=0.387).

There was no statistically significant difference in segmental wall thickness (in any of the 17 segments) in patients with and without ventricular arrhythmias. Segmental wall thickness was similar in patients with and without LGE as well.
87.5% of patients without LGE did not have documented ventricular arrhythmias. 44% of patients with LGE had documented ventricular arrhythmias compared with 12.5% of patients without LGE. (Fig 3) Conversely, 73.3% of patients with ventricular arrhythmias had LGE positivity compared to 33.3% of patients without ventricular arrhythmias (p = 0.007).

![Correlation between LGE and ventricular tachyarrhythmias](image-url)

**Figure 3**
Three out of 5 patients with maximal Left ventricular wall thickness $>30$mm had documented ventricular arrhythmias compared to 12 out of 52 patients with maximal left ventricular wall thickness $<30$mm (Fig 4).

![Correlation between maximum ventricular wall thickness and ventricular tachyarrhythmias](image)

Figure 4
44% of patients with family history of Sudden cardiac death had documented ventricular arrhythmias compared to 20% of those without family history of sudden cardiac death (p=0.06) (Fig 5).
38.5% of patients with history of syncope had documented ventricular arrhythmias compared to 22.7% of those without history of syncope (p=0.26). (Fig 6)

**Correlation between syncope and ventricular tachyarrhythmias**

- Ventricular arrhythmias+ (38.5% vs 22.7%)
- Ventricular arrhythmias- (61.5% vs 77.3%)

*Figure 6*
Odds ratio for occurrence of ventricular arrhythmias was highest for LGE by cMRI compared to traditional risk factors. (Fig 7)
Patients with ventricular arrhythmias showed LGE in more number of segments compared with patients not having ventricular arrhythmias (6.4 ± 5.8 Vs 2.5 ± 5.1, p=0.019). Generation of ROC curve showed that presence of LGE in ≥4 segments was associated with occurrence of ventricular arrhythmias with a sensitivity of 73% and specificity of 76% (Area under ROC curve 0.733). (Fig 8)
Discussion
**DISCUSSION**

Over a period of 18 months we screened 81 patients with hypertrophic cardiomyopathy and 57 patients were included in final analysis. The age of patients ranged from 5 years to 72 years with mean age 42.3 ± 18.4 years. Majority were males (73.7% were males and 23.6% were females).

Most were symptomatic. Only 17.5% were totally asymptomatic – these patients came to medical attention during routine ECG evaluation or as part of family screening in patients who were already diagnosed with hypertrophic cardiomyopathy of suffered sudden cardiac death. Dyspnoea on exertion, typical angina, atypical chest pain, syncope, presyncope and palpitations were the symptoms. Dyspnoea on exertion was most common symptom present in 59.6%. Most were in NYHA FCII DOE. Only 4 patients had NYHA FCIII DOE. All 4 had significant LVOTO. Palpitations were present in 36.8% of patients. 6 patients had history of resuscitated SCD or documented sustained ventricular tachycardia.
Family history of SCD in first degree relatives was present in 28.1% of patients. Most of these patients were not evaluated as part of family screening following SCD in family. But these events were picked up retrospectively during screening of these patients included in the study. This may reflect the lack of proper autopsy procedures in unexplained SCD in general population even in young population in India. This also puts the appropriateness of family history of SCD for risk stratification in question, because the underlying diagnosis in the patients who suffered SCD is unclear.

There was no statistical difference between patients with and without sustained or nonsustained ventricular tachycardia with regard to age, sex, presence or absence of symptoms, nature of symptoms, family history of SCD and segmental wall thickness. Similarly patients with and without LGE were also evenly matched with regard to age, sex, symptoms, family history of SCD and LV segmental wall thickness.

LGE was more common in basal anteroseptal and mid anteroseptal and mid inferoseptal segments. This held true for patients with and without ventricular tachyarrhythmias.
Sustained or nonsustained ventricular tachycardia was documented in 15 of 57 (26.3%) patients. LGE was present in 25 of 57 (43.9%) patients. It was also shown that LGE was present in 11 of 15 (73.3%) patient with documented ventricular arrhythmias, whereas only 14 of the 42 (33.3%) patients with ventricular tachyarrhythmias had LGE. Conversely, 11 out of 25 (44%) patient with LGE had ventricular tachyarrhythmias, whereas only 4 of 32 (12.5%) patients without LGE had ventricular tachyarrhythmias. The incidence of ventricular tachyarrhythmias in LGE positive patients was slightly higher in our study compared to previously published data of (44% vs 27%). But the occurrence of ventricular tachyarrhythmias in LGE negative patients were similar (12.5% vs 8.5%). While presence of LGE was not predictive of ventricular tachyarrhythmias (positive predictive value of 44% only), it can be inferred that the chance of ventricular tachyarrhythmias occurring in a patient without LGE is minimal (negative predictive value of 87.5%). This data is supportive of the premise that myocardial fibrosis is the substrate for ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy. Ventricular tachyarrhythmias may not be documented in a short 24 hour ambulatory recording of ECG; but the presence of LGE is not variable on a day to day basis and may be used as
Discussion

surrogate risk marker of patients at risk for ventricular tachyarrhythmias. The progression of LGE in patients with hypertrophic cardiomyopathy over months to years is not clear and frequency of MRI study for risk stratification has to be defined.

Extent of LGE as defined by the number of segments showing this finding was also more in patients with sustained or nonsustained ventricular tachycardia compared to patients without sustained or nonsustained ventricular tachycardia. This finding also lends credence to the hypothesis that ventricular tachyarrhythmia are more common in patients with more myocardial fibrosis. It was also showed that presence of LGE in $\geq 4$ segments predicted occurrence of sustained or nonsustained ventricular tachycardia with a sensitivity of 73% and specificity of 76%. This was a better predictor compared to LV wall thickness where ROC analysis showed best correlation at. LV wall thickness of more than 22.85mm predicted sustained or nonsustained ventricular tachycardia with a sensitivity of 53% and specificity of 71% only. The presence of LGE had no association with LV wall thickness.

Presence of LGE did not correlate with any symptoms including breathlessness. It also did not correlate with presence of LVOTO. This is
probably an attestation to the fact that myocardial fibrosis in hypertrophic cardiomyopathy is related to inherent genetic mutations causing myocardial disarray rather than scaring related to myocardial ischemia due to supply demand mismatch.

LGE was also more common in relatively younger population though this was not statistically significant. Whether this indicates that patients who do not have LGE at a younger age will not develop it as time progresses is not known. It could be also related to the fact that SCD is more common in younger age group and patients with LGE have more attrition related to SCD occurring at younger age.
Conclusions
LIMITATIONS

It was a single centre study conducted in a tertiary care centre. Referral bias may have contributed to increased incidence of documented ventricular tachyarrhythmias in this study population. Extent of LGE was correlated according to number of LV segments involved and not according to the amount of myocardium involved. Hard clinical endpoints like cardiac mortality, appropriate ICD shocks etc were not studied in this study. Patients were or various medications prior to and during MRI and 24 hour ambulatory ECG recordings and whether presence of any particular drug alters MRI or 24 hour ambulatory ECG recording findings is unknown.
Conclusions
CONCLUSIONS

In patients with HCM, ventricular arrhythmias by 24-Hour ambulatory ECG monitoring and LGE on cMRI tend to correlate.

Presence of LGE in ≥ 4 segments in cMRI predicts occurrence of ventricular arrhythmias with high degree of sensitivity and specificity.

Absence of LGE on cMRI carries a high negative predictive value for ventricular arrhythmias.

With its high negative predictive value for ventricular arrhythmias, assessment of LGE by cMRI could have an incremental value in risk stratification of patients with HCM.
Limitations
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Abbreviations
ABBREVIATIONS

CAD : Coronary Artery Disease

cMRI : Cardiac Magnetic Resonance Imaging

DOE : Dyspnoea on exertion

HCM : Hypertrophic cardiomyopathy

ICD : Implantable Cardioverter Defibrillator

LGE : Late Gadolinium Enhancement

LV : Left ventricle

LVOTO : Left Ventricular Outflow tract Obstruction

NYHA : New York Heart Association

SCD : Sudden Cardiac Death