Original Article

3D speckle tracking echocardiographic strain pattern in Hypertrophic Cardiomyopathy and its relation with Sudden Cardiac Death risk markers

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1. Background

Hypertrophic Cardiomyopathy (HCM) is one of the most common genetic cardiovascular diseases. Several epidemiological studies reported the prevalence of HCM in the general population as 1:500, and more recent studies claim that the prevalence is, even more reaching up to 1:200. Clinically HCM may have protean presentations; Sudden Cardiac Death (SCD) in young “healthy” individual is the most devastating among this. Its incidence is 0.7-1% per annum. Insertion of Implantable Cardioverter Defibrillator (ICD) has been the treatment of choice for HCM patients, who had documented VT/VF or resuscitated cardiac arrest in the past. ICD insertion as a primary prophylaxis intervention is also advised for high-risk HCM patients. This risk stratification is based on various clinical risk markers and imaging parameters, but they still lack accuracy.

Two major society guidelines to identify high risk HCM patients are AHA ACC 2011 and ESC 2014 guidelines. The former identifies six established risk markers and three potential risk modifiers for SCD in HCM patients that includes 1) Prior cardiac arrest or...
sustained VT, 2) Family history of HCM related sudden death in first-degree relatives, 3) Unexplained syncope, 4) Maximum LV wall thickness more than 30 mm, 5) Non sustained VT (NSVT) on Holter, 6) Abnormal exercise BP response. Late Gadolinium Enhancement (LGE) more than 15% of left ventricular mass, left ventricular apical aneurysm, and left ventricular outflow tract (LVOT) obstruction are the potential risk modifiers. ESC-2014 guidelines instead have devised an SCD risk formula for primary prevention. The HCM -SCD risk formula gives the probability of SCD risk over the next 5 years. This composite risk score takes into consideration of patient’s age, left atrial diameter (mm), maximal wall thickness (mm), maximum LVOT gradient, family history SCD, NSVT, and unexplained syncope. ESC-2014 guidelines recommended primary ICD insertion based on the risk score.

The evolution of new technologies like 3D echocardiography and 3D speckle tracking echocardiography (3D STE) strain has revolutionized the assessment of cardiac performance from a mere assessment of 2D imaging and ejection fraction to a more sophisticated appraisal of regional cardiac mechanics. These advances have facilitated preclinical diagnosis, refined risk stratification, and furthered our understanding of existing therapies for HCM. Among the various deformation parameters, the longitudinal strain is the most studied and has shown consistent results. For example, the Lower Global longitudinal strain (GLS) and segmental longitudinal strain dispersion time have shown a positive correlation with the incidence of ventricular arrhythmias in HCM patients. In this study, we have analysed the various 3D STE Strain parameters of HCM patients and compared their relations with the conventional SCD risk markers among them.

2. Materials and methodology

2.1. Study population

The study was conducted at a tertiary care hospital in Kerala, India. The study was approved by the institutional ethics committee, and each participant had given a written informed consent. Patient recruitment was completed over a period of one year from December 2016 to December 2017. All patients between 18 and 60 years of age attending and diagnosed to have HCM according to AHA 2011 criteria having normal 2D echocardiography report, and each participant had given a written informed consent. The study was approved by the institutional ethics committee. The study was conducted at a tertiary care hospital in Kerala, India. The study was approved by the institutional ethics committee, and each participant had given a written informed consent. Patient recruitment was completed over a period of one year from December 2016 to December 2017. All patients between 18 and 60 years of age attending and diagnosed to have HCM according to AHA 2011 criteria having normal 2D echocardiography report, and each participant had given a written informed consent.

2.2. Study methodology

After enrolment into the study cohort, past medical history was taken to know the presence of conventional SCD risk factors like un-explained syncope, resuscitated cardiac arrest and family history of SCD in first degree relatives. 24 h Holter monitoring was carried out to assess the occurrence of NSVT in all patients. The hypotensive BP response during exercise >20 mm Hg drop from peak exercise pressure or >20 mm Hg pressure drop during exercise from baseline10,11,12) was recorded in 48 patients excluding those having a history of cardiac arrest. Maximal symptom-limited exercise testing and blood pressure recording were done using a Modified Bruce protocol. In patients who were unable to proceed to stage II in Modified Bruce protocol, the 6-min walk test was done. After history taking and 2D echo the ESC SCD risk score was calculated for each HCM patient utilizing the online formula. All patients were followed up for a period of one year. The maximum follow period was 18 months. Over the telephone enquiry for syncope, resuscitated cardiac arrest and SCD was done six monthly and patients were also encouraged to report any significant events voluntarily.

2.3. Two -dimensional echocardiography

The detailed baseline 2D echocardiography was performed in both patients and their age and gender matched controls. The pattern of myocardial hypertrophy, 2D ejection fraction (EF), Left ventricular outflow tract obstruction (LVOTO), Systolic anterior motion (SAM) of the mitral valve, Mitral regurgitation, Left atrial size, and ventricular aneurysm was recorded. Modified Simpson method was used to calculate the EF in both HCM patients and healthy controls. The apical four-chamber views were used to know the LV apical aneurysm, the wall thinning and paradoxical ballooning of thinned out the area during systole was assessed. The 2D echocardiography was performed in this cohort as per ACC/AHA 2011 and 2014 ESC guidelines for HCM using the Vivid E9 system.

2.4. 3D speckled tracking echocardiography

It was recorded using the same Vivid E9 system (GE Healthcare, Horten, Norway) in HCM patients and their controls. GE’s EchoPAC version 113 software and 4D imaging protocol were used to record the Global LV strain parameters. 4D Strain integrates speckle-tracking with three-dimensional echocardiography, enabling the computation of all LV Strain components from a single apical LV 4D data set. In comparison with two-dimensional (2D) speckle-tracking, 4D Strain seems potentially more apt to capture the complex LV deformation with no issues related to the “out-of-plane” motion of speckles or the need to interpolate the whole LV myocardium from the partial information contained in three thin slices of the LV. ECG gating and frame rate of at least >25 were set as standard. A good four-chamber view was taken and recorded with maximum breath holding capacity possible for the patient. Finally, the data acquired was processed offline and global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), global area strain (GAS) and segmental strains were calculated. The detailed 4D imaging protocol is provided in Annexure-1.

2.5. Reproducibility

To know the intra-operator variability, two sets of strain values were calculated for each patient and their control from two different 3D echo images recorded within a 24 h time period. Another experienced independent operator who had been blinded for the details of cases and controls repeated the 3D echo and offline deformation analysis in all HCM patients and their healthy controls. This was done to assess the inter-operator variability of strain values.

3. Statistical analysis

Continuous and qualitative variables were expressed as mean with standard deviation (SD), and discrete variables were expressed as absolute numbers and percentages. Paired Student’s t-test was used for comparisons of independent samples and was used for comparison of means. Independent sample t-tests were used for subgroup analysis. Linear correlations were evaluated
between LV strains and ESC SCD risk score and other continuous variables using the Pearson test. Interobserver and intraobserver variability were assessed by the intraclass correlation coefficient. All statistical tests were 2-tailed; p-value < 0.05 was considered significant. All statistical tests were carried out in the IBM-SPSS 22 (SPSS Institute, Chicago, IL, USA).

4. Results

Out of the 82 patients screened for selection into the study, eight patients were excluded as they had evidence of CAD (Three patients had AWMl, three had critical lesions in CAG and two had IVMl). Six patients had atrial fibrillation (AF) and one had frequent VPCs. Ten patients had been excluded due to poor quality echo window and seven patients had poor 3D image. Finally, after excluding 32 patients altogether 50 patients were enrolled for the analysis.

4.1. Baseline characters

The baseline characteristic of HCM patients and controls were comparable except for EF and heart rate (Refer Table 1). The predominant pattern of involvement of hypertrophy was asymmetrical septal hypertrophy. Most of the patients were in NYHA class I/II. Most prevalent risk markers were LVOT obstruction followed by family history of SCD and presence of maximum LV wall thickness of more than 30 mm. NSVT and abnormal blood pressure response were seen in three patients each. There were eight patients having more than one conventional risk markers in the study cohort and three patients had three risk markers clustered in them. Twenty-six patients had systolic anterior motion (SAM) of the anterior mitral leaflet (AML) and twelve patients had more than mild mitral regurgitation.

The ESC SCD risk score was calculated for forty-eight patients as two patients already had a history of resuscitated cardiac arrest. It is a risk scoring system which takes into consideration of the patient’s age, maximal left atrial size, maximum LV thickness, the maximum LVOT gradient, the presence of family history of SCD in first degree relatives, the presence of NSVT in Holter and presence of unexplained syncope in the past. The ESC risk score is supposed to give the probability of SCD over the next five years. In the study cohort, two patients had a score of more than six which warrant the insertion of ICD for primary prophylaxis. Five patients had a score of more than four and less than six. Majority of the patients (Forty-one out of forty-eight) had a low score.

4.2. Deformation parameters of HCM patients

All the deformation parameters of HCM patients were significantly lower compared to age and gender-matched healthy controls. The detailed observations are depicted in Table 2.

4.3. SCD risk markers and 3D STE deformation

To study the relationship between various risk markers and 3D STE strain parameters two groups were created within the study cohort of HCM patients and compared using appropriate statistical tests depending on the nature of variable (Refer Table 3).

There were ten patients with a family history of SCD in the patient cohort. When on comparing the various strain parameters between patients with and without a family history of SCD, it was found that GLS, GRS, and GAS were significantly low in patients with a family history of SCD. GCS even though found to be low in those with a family history of SCD was not significant statistically. There were seven patients with a maximum LV wall thickness of more than 30 mm in the patient cohort. All the strain parameters (GLS, GCS, GRS, and GAS) were significantly low in patients with LV wall thickness of more than 30 mm. The absolute value of the maximum LV wall thickness was then compared with the various strain parameters using the Pearson correlation coefficient. There was a significant inverse correlation with the absolute value of all strain parameters (Table 4). Three patients had NSVT in Holter test and these patients had a low value for all strain parameters but not significant statistically. The exercise test was done in forty-eight patients and three had an abnormal response as defined in the methodology. These three patients had all the strain parameters detected low and were statistically significant when compared to

| Parameters | HCM patients | Healthy controls | p value |
|------------|--------------|------------------|--------|
| GLS        | -7.30        | -18.78           | <0.001 |
| GCS        | -11.26       | -25.08           | <0.001 |
| GRS        | 20.56        | 39.70            | <0.001 |
| GAS        | -14.80       | -29.34           | <0.001 |

Table 1
The baseline characteristics of HCM patients and healthy age and gender-matched controls.

| Parameters | HCM patients (50) | Controls (50) |
|------------|-------------------|---------------|
| Age        | 46.16             | 46.87         |
| Gender(M:F)| 38:12             | 38:12         |
| EF         | 69.12             | 71            |
| Heart rate | 60                | 69            |
| Systolic blood pressure | 126 | 118 |
| Diastolic blood pressure | 84 | 76 |
| Pattern of hypertrophy | Ash | Apical |
| Presence of LVOT gradient | Presence of significant Mitral regurgitation | Presence of SAM | LVIDD | ESC SCD risk score | Presence of LVOT gradient | Presence of significant Mitral regurgitation | Presence of significant Mitral regurgitation | Presence of significant Mitral regurgitation | Presence of significant Mitral regurgitation |
| LA size | 35.94 | 30 |
| Presence of LVOT gradient | 25 | 29 |
| Presence of significant Mitral regurgitation | 12 | 12 |
| Presence of SAM | 26 | 26 |
| LVIDD | 39 | 32 |
| ESC SCD risk score | >6 | 2 |
| 4–6% | 5 | - |
| <4% | 41 | - |

Table 2
Comparing various deformation parameters between HCM patients and healthy age and gender-matched volunteers.
those of patients with a normal response to exercise. There were twenty-five patients with significant LVOT gradient and all the strain parameters were significantly lower in these patients. There were twenty-six patients with SAM of AML in this group and all the strain parameters were low in those having SAM with a statistically significant difference with respect to GLS, GRS, and GAS. Twelve patients had significant MR out of the twenty-six and all of them had lower strain parameters compared to those without MR. This difference was significant only for GLS. Patients with unexplained syncope, resuscitated cardiac arrest and LV aneurysm were found to have low deformation parameters, but as patients with these risk markers were less, no meaningful statistical conclusions could be made. Nine patients had a pure apical type of HCM and they had better GLS values compared to the non-apical variety of HCM. There were eight patients having more than one conventional risk markers. These patients had lower values of all strain parameters and that was also statistically significant.

Age and left atrial size had no significant correlation with any of the deformation parameters in this study (Table 4).

### 4.5. Reproducibility

The reproducibility of the 3D strain parameters was assessed using the ICC (Intra-class Correlation Coefficient). The ICC test was done in all HCM patients and in their healthy controls. In HCM patients and in their healthy controls all the strain values showed excellent intra and inter-operator reproducibility (Table 5).

### 4.6. Follow up

Five patients lost follow and in all others at least one year follow up was done, maximum follow up period was 18 months and minimum one year. There were two deaths due to non-cardiovascular causes (One due to sepsis and the other due to malignancy). Only one significant event recorded. It was syncope in a patient who has the following strain values and ESC-SCD risk score (GLS -5; GCS -7; GRS 14 and risk score of 4.77).

### 5. Discussion

Strain studies are crucial in studying the segmental and global myocardial mechanics in patients with HCM, as most of them would have normal or falsely increased 2D ejection fraction (EF). Strain abnormalities tend to precede the EF change. EF is not considered to be a robust predictor the risk in HCM patients. In this study cohort, six patients had NYHA class III/IV symptoms, and the rest were in NYHA class I/II. The mean age of this cohort was 46.16. All patients in this cohort had a normal 2D EF. These baseline characters were almost similar to previous studies.

### Table 3

| Association between various SCD risk markers and deformation parameters compared with the independent sample t-test. |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group | GLS | Sig | GCS | Sig | GRS | Sig | GAS | Sig |
| Family history of SCD | Yes-10 | -4.10 | 0.01 | -9.90 | 0.01 | 12.50 | 0.01 | -9.40 | 0.01 |
| LV wall thickness >30 mm | No-40 | -8.10 | 0.01 | -11.60 | 0.01 | 22.58 | 0.01 | -16.15 | 0.01 |
| Abnormal exercise test | Yes-7 | -4.00 | 0.01 | -9.14 | 0.01 | 11.00 | 0.01 | -5.42 | 0.01 |
| No-43 | -7.84 | 0.01 | -11.60 | 0.01 | 22.12 | 0.01 | -8.86 | 0.01 |
| No-45 | -7.56 | 0.01 | -11.44 | 0.01 | 21.31 | 0.01 | -15.22 | 0.01 |
| NSVT | Yes-3 | -5.67 | 0.01 | -8.33 | 0.01 | 15.00 | 0.01 | -12.00 | 0.01 |
| No-47 | -7.40 | 0.40 | -11.45 | 0.05 | 20.91 | 0.27 | -14.98 | 0.40 |
| LVOT gradient at rest | Yes-25 | -5.60 | 0.01 | -10.44 | 0.01 | 16.60 | 0.01 | -11.96 | 0.01 |
| No-25 | -9.00 | 0.01 | -12.65 | 0.03 | 24.52 | 0.01 | -17.64 | 0.01 |
| SAM | Yes-26 | -6.04 | 0.01 | -10.58 | 0.01 | 17.73 | 0.01 | -12.69 | 0.01 |
| No-24 | -8.67 | 0.01 | -12.00 | 0.06 | 24.63 | 0.01 | -17.08 | 0.01 |
| Significant MR | Yes-12 | -5.58 | 0.01 | -9.92 | 0.01 | 17.08 | 0.01 | -12.25 | 0.01 |
| No-38 | -7.84 | 0.04 | -11.68 | 0.05 | 21.66 | 0.12 | -15.61 | 0.08 |
| Unexplained syncope | Yes-2 | -5.50 | 0.39 | -9.50 | 0.52 | 16.50 | 0.52 | -10.50 | 0.29 |
| No-48 | -7.38 | 0.45 | -11.33 | 0.52 | 20.73 | 0.52 | -14.98 | 0.52 |
| Resuscitated cardiac arrest | Yes-2 | -8.00 | 0.77 | -12.50 | 0.77 | 22.00 | 0.77 | -17.00 | 0.59 |
| No-48 | -7.27 | 0.77 | -11.21 | 0.52 | 20.50 | 0.52 | -14.71 | 0.52 |
| LV aneurysm | Yes-1 | -4.00 | 0.34 | -10.00 | 0.65 | 20.00 | 0.95 | -12.00 | 0.64 |
| No-49 | -7.37 | 0.34 | -11.29 | 0.24 | 20.57 | 0.24 | -14.86 | 0.52 |
| Pattern of hypertrophy | Apical-9 | -9.33 | 0.04 | -12.33 | 0.20 | 24.78 | 0.12 | -18.22 | 0.52 |
| Nonapical-41 | -6.85 | 0.04 | -11.02 | 0.20 | 19.63 | 0.20 | -14.05 | 0.52 |
| More than one SCD risk marker | Yes-8 | -3.88 | 0.01 | -9.13 | 0.02 | 10.75 | 0.01 | -8.75 | 0.01 |
| No-42 | -7.95 | 0.01 | -11.67 | 0.01 | 22.43 | 0.01 | -15.95 | 0.01 |

### Table 4

| Correlation with continuous variables and strain parameters. |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variables | GLS | p value | GCS | p value | GRS | p value | AS | p value |
| ECS SCD risk score | 0.496 | <0.001 | 0.491 | <0.001 | -0.529 | <0.001 | 0.519 | <0.001 |
| Absolute maximum LV wall thickness | No-45 | -0.576 | <0.001 | 0.595 | <0.001 | -0.680 | <0.001 | 0.672 | <0.001 |
| LA size | No-38 | 0.223 | 0.119 | 0.114 | 0.431 | -0.207 | 0.149 | 0.188 | 0.191 |
| Age | -0.005 | 0.973 | 0.01 | 0.934 | 0.01 | 0.995 | -0.018 | 0.901 |
It was observed in previous studies that all the strain parameters were significantly reduced in HCM patients. Later studies showed that there was a compensatory increase in global circumferential strain compared to reduced global longitudinal strain in early stages of HCM. Once the disease progresses, this compensation seems to get exhausted and all strain parameters tend to fall.

The EACVI NORRE study had given the normal reference range of the 3D strain parameters. It was found that all strain components were higher in women than in men. The lower range was 18.6% in men and 19.5% in women for 3D GLS, 27.0% and 27.6% for 3D GCS and 36.8% and 40.7% for 3D GRS, respectively.

In our study, all the global strain parameters were significantly low in HCM patients compared to normal healthy controls. This finding had excellent intra and inter-operator reproducibility also. The compensatory increase in GCS was not observed in the study. The role of medication in this finding was not assessed as all these patients were on beta blockers.

Research utilizing deformation characteristics with emphasis on SCD predictability in HCM patient is very few. Urbano-Moral et al had studied the relation of GLS, GCS, and GRS with that of LV wall thickness and compared the same with LGE at the hypertrophied segments. In that study it was found that these global strain parameters were found to be low in areas where LV thickness was more than 15 mm or more and in these areas, the LGE percentage was also found to have high concentration. Another study by Debonnaire et al demonstrated that GLS less than −14% and a left atrial indexed volume more than or equal to 34 mL/m2 were independent predictors of appropriate ICD therapy during follow-up. Later Haland et al demonstrated that HCM patients with ventricular arrhythmia had worse GLS than the control HCM patients. While Marie-Philippe Vergé et al showed that in line with GLS, basal longitudinal strain, and longitudinal strain in the hypertrophic area are valuable parameters for evaluating risk stratification in HCM. Mean longitudinal strain in the hypertrophic area, in particular, appears more predictive of SCD occurrence and appropriate ICD shocks than GLS.

In this study, the conventional risk markers were related to the global strain parameters. The two most common conventional risk markers in this cohort were a family history of SCD and LV aneurysm with that to the strain parameters. These findings emphasize the possibility of a linear association between conventional SCD risk markers and deformation parameters in HCM, which warrant further research.

In this study the left atrial size and age of the patients were found to have no significant correlation with all global strain parameters, the LA volume index (LAVI) was not assessed in this study and the authors suggest LAVI would be a better parameter compared to 2D parasternal long axis left atrial size. The relatively better global strain values in Apical HCM compared to those of non-apical HCM also warrant further studies. Some case reports had identified paradoxical strain (means systolic lengthening of apical

### Table 5

| Strain parameter | Intra-operator Variability | p-value | Inter-operator Variability | p-value |
|------------------|---------------------------|---------|---------------------------|---------|
| GLS              | 0.914 (0.85–0.951)        | <0.001  | 0.758 (0.610–0.855)       | <0.001  |
| GCS              | 0.763 (0.617–0.858)        | <0.001  | 0.401 (0.140–0.609)       | 0.002   |
| GRS              | 0.670 (0.48–0.798)         | <0.001  | 0.670 (0.483–0.798)       | <0.001  |
| AS               | 0.928 (0.87–0.958)         | <0.001  | 0.742 (0.586–0.845)       | <0.001  |
hypertrophied segments instead of shortening) in apical HCM segments and relatively normal strain parameters in mid and basal LV segments.23

6. Limitations

This is basically an observational cross-section study and has its own limitations in concluding about the quantum of linear correlation observed between conventional risk markers/score and 3D deformation parameters. The author admits that the study was underpowered for subgroup analysis and the event rate during the relatively short follow up period was also very low to comment on an arbitrary cutoff for strain rate to predict SCD risk. The overall outcome from the study warrants future large prospective studies especially for risk stratification. The effects of medications were not taken into consideration. As all the patients in this cohort were on a beta blocker subgroup analysis was not possible. Sub optimal echo window was still a matter of concern in a few cases even though most of such cases were excluded from the study prior to enrolment. The technical feasibility of 3D STE study was 67% only. 24 out of 74 patients were excluded from the study due to technical difficulty in 3D STE strain analysis. The main reason for exclusion was inadequate echo window, arrhythmia (AF) and inability to maintain breath holding. This study did not compare the strain parameters to the quantum of scar on LGE by cardiac MRI.

7. Conclusions

All 3D deformation parameters are found to be low in HCM patients compared to controls. There exist a possible linear correlation between conventional SCD risk markers and 3D deformation parameters, which may be utilized for risk stratification and SCD predictability in HCM patients after confirmation with larger prospective studies.

What IS already KNOWN about this research

SCD risk estimation in HCM patients still lacks an accurate predictor. The role of novel 3D deformation technique in this regard is still evolving. It has been shown that Longitudinal strain is consistently reduced in HCM patients. The perceived change in deformation parameters has never been taken as a tool for SCD predictability.

What this study adds

Most of the 3D deformation parameters have a more or less linear association with other known SCD predictors. In SCD predictability the role of 3D deformation parameters has to be subjected to more prospective studies.

Appendix – 1

4D imaging protocol for GE’s EchoPAC version 113 software.

- 3D image acquisition
  - Select 4Vprobe
  - ECG GATING IS A MUST FOR 4D IMAGING
  - Select the volume size LARGE for a FULL VOLUME acquisition
  - Acquire a 4D LARGE VOLUME image with MULTI-BEAT until the frame rate is higher than 25 or at least 40% of patient heart rate.
  - Store this image by pressing IMAGE STORE twice.
- 3D STE offline analysis
  - Press MEASURE on the control panel, select VOLUME, and then 4D AUTO LVQ.
  - Press EDV, mark two points— base of MV and the apex.
  - Press ESV, mark the same two points again.
  - Press Volume Waveform. The machine will generate the LV 4D Shell model.
  - Then click on LV MASS, the machine will trace the outer myocardial border, and compute the 4D LV MASS.
  - Select 4D Strain ROI, and select 4D STRAIN RESULTS.
  - The machine will take 20–30 s, and shall display the 4D strain curves as well as the Bulls–eye plot for 4D strain.
  - By default, LONGITUDINAL 4D STRAIN shall be displayed first.
  - By clicking on the LONGITUDINAL STRAIN button on the touch-screen, the CIRCUMFERENTIAL, AREA and RADIAL Strain shall also be displayed with the respective curves and the Bulls–eye plot.
  - By pressing the ES (end systolic) point on strain curve, the averaged respective Strain values for all the segments and global strain valves can be obtained.
  - Select APPROVE & EXIT to approve the results and exit the application.

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