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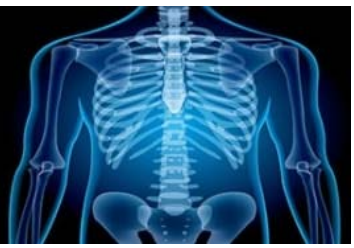

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Added value of native T_1 mapping and extracellular volume fraction to late gadolinium enhancement in hypertrophic cardiomyopathy

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Abstract
Background: Cardiac MRI allows for non-invasive and precise myocardial fibrosis evaluation within individuals having hypertrophic cardiomyopathy. Although myocardial native T_1 mapping can quantify diffuse interstitial fibrosis, late gadolinium enhancement MRI can only identify focal fibrosis.
Aim: The study objective was estimation of myocardial T_1 mapping efficacy and calculated extracellular volume in differentiating segments with and without late gadolinium enhancement in individuals having hypertrophic cardiomyopathy.
Patients and Methods: Our study involved 38 individuals diagnosed or suspected to be hypertrophic cardiomyopathy patients and a control group of ten individuals with no underlying health issues as a reference for native T_1 values and extracellular volume. Cardiac MRI was performed for all subjects. Magnetic resonance scans comprised localizing white / black blood images, cine scans, native T_1 mapping, late gadolinium enhancement and post contrast T_1 mapping scans.
Results: The native T_1 was significantly longer in hypertrophic cardiomyopathy patients than in control subjects at all-time points (1049.048 ±50.930 ms) (938.106 ±36.368 ms) (p<0.01) with a cutoff value of 1066 ms for myocardial fibrosis identification (a sensitivity of 74%, a specificity of 82%, and an accuracy of 85%). Also, extracellular volume was significantly greater within patients having hypertrophic cardiomyopathy (29.359±5.501ms) compared with controls (24.823±1.876 ms) (p<0.02) with a threshold of 28% for fibrosis evaluation (a sensitivity of 53%, a specificity of 98%, and an accuracy of 78%).
Conclusions: Native T_1 values and extracellular volume show benefits while detecting and quantifying diffuse interstitial myocardial fibrosis not well visualized by late gadolinium enhancement MRI.

Keywords: Hypertrophic cardiomyopathy, native T_1 mapping, extracellular volume fraction, MRI

Introduction
Hypertrophic cardiomyopathy represents a popular reason of sudden cardiac death in young population [1]. Myocardial fibrosis is often responsible for pathophysiology of abrupt death in individuals having HCM. So, detection of myocardial fibrosis can aid in setting the optimal treatment strategies and ameliorating prognosis in hypertrophic cardiomyopathy patients [2, 3]. By echocardiography, HCM is diagnosed when where the myocardial wall thickening at end diastole is fifteen mm or more elsewhere in the left ventricle and after exclusion of hypertrophy common etiologies as aortic stenosis, hypertension, infiltrative diseases (amyloidosis) and renal disorders. Myocardial thickness of twelve mm or more at left ventricular wall necessitate evaluation, particularly in individuals having a positive family history [4]. Recently, MR imaging has an emerging function in estimation of HCM phenotype. It is a method of choice providing precise measurements of maximal wall thickness to facilitate diagnosis of myocardial hypertrophy even its subtle forms. Also, it can identify massive left ventricular hypertrophy and extensive areas of myocardial fibrosis portending disease progression [5]. LGE-MRI can precisely recognize focal myocardial fibrosis to differentiate between ischemic and non-ischemic heart disease. Although it can reveal regional variance in myocardial enhancement in relation to nulled normal myocardium, it hardly detect subtle diffuse myocardial enhancement [3, 6].

Myocardial native T_1 mapping represents a non-invasive technique quantifying diffuse myocardial aberrations with no necessity for any assumed normal tissue areas. ECV, measured utilizing pre- and post- T_1 mapping, identifies diffuse myocardium anomalies regarding different disorders. Many studies have realized that T_1 mapping and ECV can distinguish individuals having HCM myocardium from healthy ones [7].

Native myocardial T_1 and ECV fraction measurements must be compared for individuals having HCM without LGE nor hemodynamic obstruction with healthy individuals to identify subtle myocardial fibrosis in HCM, this is attributed to the increased extracellular matrix as an earliest abnormality in HCM causing altered native myocardial T_1 and ECV measurements [7, 8].

Our goal was aimed at assessing myocardial magnetic resonance native T_1 time and the extracellular volume fraction (ECV) efficiency while detecting myocardial fibrosis within individuals having HCM even if not visualized in late gadolinium enhancement MRI.

Methods

Study population

Our prospective study involved thirty-eight individuals diagnosed or suspected hypertrophic cardiomyopathy. The individual received a referral from the cardiovascular department to the Radiodiagnosis one between September 2020 and September 2022. Ten subjects with no medical history were also included as a control group.

The study was executed after clarification of the procedure benefits and risks from the participants, obtaining informed consents from them as well as Research Ethics Committee (REC) approval. Private patient information was utilized only for research purposes.

Concerning patients' group, individuals were involved if diagnosed or suspected HCM by family history or echocardiography. The controls were medically-free with normal echocardiography without gender preference.

Patients were excluded when having irregularity of HR, renal malfunction (GFR< 30 ml/min/1.73 m2), morbid obesity, claustrophobia, or any contraindications to MRI examination.

All included individuals were examined by MRI

Using 1.5 Tesla Siemens machine (closed magnet). They were all injected with 0.3 mmol/Kg body weight gadolinium based contrast agent. All participants underwent an examination at the supine position, head first without movement to ensure that the planned scan area correspond to the area actually scanned.

MRI protocol

Positioning of ECG leads: Four ECG pads were positioned anterior to chest wall; two para-sternal, one apical and the other is at the anterior axillary line.

Image acquisition:

An initial scout image obtained to set field of view (FOV) by taking out heart images in three orthogonal orientations in order to plan the subsequent images.

Cine images were performed in the horizontal-long-axis (4 chamber), vertical-long-axis (2 chamber), short-axis (SAX), 3 chamber and left ventricular outflow tract (LVOT) planes utilizing SSFP sequences with retrospective ECG gating while a gentle expiratory breath-hold, (echo time [TE]/repetition time [TR]/flip-angle: 1.7 ms/3.4 ms/60°, spatial resolution 1.8 x 1.8 x 8 mm, temporal resolution ≤50 ms between phases and in-plane resolution <1.5 x 2 mm.

SAX cine images stack obtained from the mitral valve plane utilizing the apex covering ventricles. The basal cuts were recognized during end-diastole from the long axis views at the atrio-ventricular junction level. SAX stack was obtained utilizing perpendicular plane to the interventricular septum in both the two chamber and four chamber views or parallel to the mitral valve.

Hypertrophied areas detection and assessment, ejection percentage, LV mass, and LV volumes were accomplished by parallel imaging with 8 mm slice thickness and 0 mm interslice gaps (with semi-automated post processing software).

Velocity encoding (Venc) gradient echo flow imaging, also known as phase contrast imaging was used for flow quantification. At first, in-plane flow image was acquired along the blood flow direction by copying the image position from the previously obtained LVOT cine image. Adapting the Venc to the anticipated velocities was done.

Second, through plane images were then acquired; centered in the aorta, and an orthogonal alignment to the anticipated primary blood flow direction in two spatial directions and centered in the iso-center of the magnet with slice thickness 5-8 mm; in- plane resolution at least 1/10th of the vessel diameter.

T_1 mapping was done utilizing the Modified Look-Locker Inversion recovery sequence. This sequence was used to capture images before and ten to fifteen minutes following the contrast agent injection. They were obtained in short-axis and 3 chamber views, with varying inversion preparation time. The images acquisition was performed using identical conditions during the late diastole of the same cardiac phase. Dibe

Typical acquisition parameters involved: echo time (TE)/repetition time (TR) = 1.03/413.57 ms, flip angle = 35º, FOV = 450×450 mm, matrix size = 256×169, interpolated pixel size=1.8×1.8, GRAPPA = 2, 24 reference lines, cardiac delay time of 500 ms, 0.22 s acquisition time for single image, phase partial Fourier 7/8. When off-resonance artifacts free images were needed, shimming and adjustments of center frequency were proceeded.

Typical imaging parameters involved: non-selective inversion pulse, steady state free precession single-shot read out in mid-diastole, minimum inversion time of ninety minutes, inversion time increment of eighty minutes, flip angle of 35◦, 2 inversions, 5 images obtained following first inversion, three heart beats pause, and three images obtained following second inversion; the 5(3)3 MOLLI variant.

The acquisition of LGE occurred after six to ten minutes after intravenous gadolinium administration (0.3 mmol/Kg body weight) utilizing inversion recovery prepared fast gradient echo sequence. Two, three and four chamber and SAX LGE images were applied covering entire ventricle at repetition time of 6.5 minutes, echo time=3.1 minutes, inversion time= 160 to 240 minutes, matrix= 256 x 192, 8mm slice thickness with 1 mm interslice gap, FOV= 32 to 44 cm, flip angle= 20°, bandwidth= 31.2 kHz, views per segment= 24.

Post processing

Analysis of all MRI images of patients and controls was carried out using an off-line workstation; Argus (Siemens

Healthcare, Erlangen, Germany) software by two radiologists, having eleven and five yrs of expertise in cardiac MRI. They were unaware of the clinical data and laboratory indicators, and the final decisions were made through consensus then documented.

- Evaluation of LV Function through manual curing of LV short-axis epicardial and endocardial borders at end-systole and end-diastole to reach EDV, ESV, SV, EF and myocardial mass and myocardial wall thickness.
- Disease characterization by assessment of the phenotype (septal hypertrophy, symmetric or concentric, mid-ventricular, asymmetric, apical, mass-like HCMs), measuring maximum wall thickness and identifying the location.
- Assessment of pre-contrast T_1 time & Myocardial ECV by manual assessment of short-axis & 3 chamber T_1 maps images according to the 17 cardiac segments' model, a ROI >12 pixels was manually established on both pre-contrast and post-contrast images in each segment of the basal, mid-ventricular and apical cuts as well as the apex with 17 segments for all patients. Another ROI was delineated in both pre and post contrast images in the blood pool to get the signal shortening of the blood. Those ROIs were delineated in a blind manner without looking at the corresponding LGE images.
- Checking the presence of enhancement at LGE images at the different planes.

Statistical analysis

- Data went through a statistical analysis utilizing the SPSS (Statistical-Package-for-Social-Sciences) version 20 for Windows® (IBM-SPSS-Inc, Chicago, IL, USA).
- The Shapiro Walk test for normality was used. Qualitative data were displayed as frequencies and relative percentages. Quantitative data were displayed as mean ± SD (Standard deviation) and range. Student's t-test (t) was utilized in performing a comparison among two groups with parametric data. Receiver Operation Characteristic (ROC) curves were formed for reaching the quantitative variable diagnostic ability in categorical outcome prediction.
- Probability (P- value): significant if P- value <0.05.

Results

Our research involved thirty eight HCM patients; 50% men and 50% women, whose ages were between 13 to 64 years with a mean of 41.15± 15.26. 10 healthy volunteers as controls were also included; 60% male and 40% female, whose ages were between twenty-five to sixty years with a mean of 41.00± 14.68.

According to phenotype of hypertrophy in the studied HCM patients group, 16 patients (42.11%) had septal pattern of hypertrophy (Fig. 1), 11 patients (28.94%) had asymmetrical anti-clock wise pattern (Figure 2), 7 patients (18.42%) had concentric pattern, 3 patients (7.89%) had apical pattern and 1 patient (2.63%) had focal pattern of hypertrophy. Out of those patients, 8 patients (21.05%) had associated apical RV hypertrophy (Figure 3).

The hypertrophied segments ranged in thickness from 15 mm to 33 mm with a mean of 22.3 ±5.413 mm. The site of maximum thickness was the mid infero-septal (IS) segment in 12 patients (31.58%) (Fig 1, 2), the mid antero-septal (AS) segment in 10 patients (26.3%) (Figure 2, 3), the basal antero-septal (AS) segment in 7 patients (18.42%), the mid anterior segment in 2 patients (5.26%) (Figure 4), the apical inferior segment in two (5.26%) individuals, the basal anterior segment in 1 patient (2.6%), the basal inferior segment in 1 patient (2.6%), the mid infero-lateral (IL) segment in 1 patient (2.6%), the mid antero-lateral (AL) segment 1 (2.6) patient, and the apical septal segment in 1 patient (2.6%). Some patients had the same thickness in more than one segment. There was a significant variation (P-value <0.001) among individuals having HCM and controls as regard to the myocardial mass and indexed myocardial mass as shown at table 1.

Among the studied patients with HCM, 9 patients (23.68%) had left ventricular outflow tract (LVOT) obstruction (Fig 1, 4), 11 patients (28.95%) had mid-ventricular obliteration/obstruction, while 13 (34.21%) patients had systolic anterior motion (SAM) (Figure 1, 4).

According to different volume and function parameters, significant variation was noticed among individuals having HCM and controls according to RV EDVI, RV SVI, LV EF%, LV ESV and LV ESVI compared to controls. End-systolic volume (ESV) was less, while LVEF and LV myocardial mass were greater within individuals having HCM (all $p< 0.001$) (Table 1).

Within HCM group, 26 patients (68.42%) showed patchy mid wall late gadolinium enhancement denoting macroscopic fibrosis (Figures 2, 3, 4); the mid antero-septal segment was the commonly site for fibrosis reported in 13 patients (34.21%) (Figure 3), while 12 patients (31.58%) showed no late gadolinium enhancement (Figure 1).

Native T_1 mapping was performed for all the studied subjects. There was a significant elongation in native T_1 mapping values in HCM individuals as opposed to controls as shown in table 2.

Also, a significant elongation of the native T_1 mapping values in segments with LGE was noted when compared with segments without LGE (P-value = 0.001) and this was noticed at the basal inferoseptal and inferior segments, most mid-ventricular segments, and apical septal, inferior and lateral segments. No significant elongation in native T_1 mapping values in other basal segments, antero-lateral mid-segment or apical anterior segment and apex (Table 3).

We obtained a cutoff native T_1 value of 1066 ms that can optimally differentiate segments affected by fibrosis from segments without fibrosis, with a sensitivity of 73.99%, a specificity of 82.35%, PPV of 94.1%, NPV of 45.5% and accuracy of 85.1%.

Native T_1 mapping established excellent diagnostic performance with a significant larger area-under the curve (AUC= 85.1%) as opposed to LGE– CMR (Figure 5).

After evaluation of ECV%, a significant rise in ECV% within individuals having HCM was noted compared to the controls as illustrated in Table 4.

The comparison between LGE patients (positive fibrosis) and patient without LGE and ECV% showed increased ECV% with statistical significance (P-value =0.001) in most of basal segments. No significant increase in ECV% in basal inferior and basal antero-lateral segments (Table 5)

The correlation between patients with LGE (positive fibrosis) and patient without LGE and ECV% showed increased ECV% with statistical significance (P-value = 0.001) in mid-ventricular anterior, antero-septal and infero-septal segments. No significant increase in ECV% in mid-

ventricular inferior, infero-lateral and antero-lateral segments (Table 5).

The comparison between patients with LGE (positive fibrosis) and patient without LGE according to ECV% showed no significant increase in ECV% in all apical segments (Table 5).

A cutoff value of ECV% of > 28% was obtained, it can optimally differentiate segments with fibrosis from segments without fibrosis, with a sensitivity of 52.63%, a specificity of 98.4%, PPV of 99.4%, NPV of 35.4% and accuracy of 78.3%.

ECV% showed excellent diagnostic performance with a significantly larger area under the curve (AUC= 78.3%) as opposed to LGE – CMR (Figure 6).

Table 1: Descriptive analysis comparing between the studied groups according to maximum myocardial thickness different volume and function parameters

	Group						T- Test	
	HCM patients			Controls				
	Mean	±	SD	Mean	±	SD	t	P- value
Maximum myocardial thickness (mm)	22.316	±	5.413	10.340	±	0.560	6.932	<0.001*
Myocardial mass	197.763	±	69.674	124.600	±	9.766	3.287	0.002*
Indexed myocardial thickness	111.211	±	37.256	63.200	±	10.820	4.002	<0.001*
RV EF%	64.763	±	8.378	62.000	±	6.254	0.971	0.337
RV EDV (ml)	129.605	±	35.656	149.400	±	13.818	-1.711	0.094
RV ESV (ml)	47.026	±	19.676	56.800	±	12.848	-1.483	0.145
RV SV (ml)	82.579	±	20.728	91.000	±	6.000	-1.262	0.213
RV EDVI (ml/m^2)	70.737	±	17.030	83.200	±	12.426	-2.160	0.036*
RV ESVI (ml/m^2)	25.579	±	10.477	31.600	±	7.905	-1.690	0.098
RV SVI (ml/m^2)	44.789	±	8.930	50.800	±	6.680	-1.981	0.054*
LV EF%	71.500	±	9.238	60.400	±	5.719	3.605	0.001*
LV EDV (ml)	131.132	±	39.659	148.000	±	17.153	-1.305	0.198
LV ESV (ml)	38.947	±	25.470	59.400	±	15.153	-2.417	0.020*
LV SV (ml)	92.289	±	22.808	88.600	±	4.742	0.505	0.616
LV EDVI (ml/m^2)	71.447	±	18.127	81.400	±	11.207	-1.648	0.106
LV ESVI (ml/m^2)	21.237	±	12.902	32.600	±	9.009	-2.613	0.012*
LV SVI (ml/m^2)	50.263	±	9.235	48.400	±	1.713	0.630	0.532

T= Student t-test

P- value: probability.

*: p- value (< 0.05) is significant.

Table 2: Comparison between HCM patients group and control group according to native T_1 mapping values.

Native T_1 mapping values (msec)	Group						T- Test	
	HCM patients			Controls				
	Mean	±	SD	Mean	±	SD	t	P- value
Basal A	1048.263	±	50.962	968.800	±	39.268	4.573	<0.001*
Basal AS	1055.974	±	52.075	1001.800	±	41.992	3.033	0.004*
Basal IS	1055.132	±	51.829	987.600	±	28.139	3.949	<0.001*
Basal I	1053.711	±	59.551	990.800	±	51.179	3.051	0.004*
Basal IL	1053.921	±	62.537	989.000	±	33.427	3.149	0.003*
Basal AL	1052.474	±	50.752	980.000	±	22.081	4.380	<0.001*
Mid A	1047.684	±	47.130	990.600	±	34.830	3.570	0.001*
Mid AS	1057.474	±	47.375	1012.400	±	38.785	2.768	0.008*
Mid IS	1055.553	±	43.220	982.800	±	31.864	4.963	<0.001*
Mid I	1047.605	±	38.069	983.000	±	28.245	5.000	<0.001*
Mid IL	1034.789	±	38.863	949.400	±	32.942	6.360	<0.001*
Mid AL	1033.553	±	33.284	981.000	±	27.236	4.593	<0.001*
Apical A	1031.053	±	72.032	977.000	±	42.111	2.262	0.028*
Apical S	1057.474	±	50.838	993.000	±	52.358	3.547	0.001*
Apical I	1047.658	±	52.817	953.200	±	54.006	5.010	<0.001*
Apical L	1050.211	±	53.331	981.800	±	40.455	3.769	<0.001*
Apex	1051.289	±	61.204	990.600	±	19.352	3.074	0.004*
Average	1049.048	±	50.930	938.106	±	36.368	3.944	0.001*

T= Student t-test

P- value: probability.

*: p- value (< 0.05) is significant.

Table 3: Comparison between mean values of native T_1 mapping as regard late contrast enhanced imaging for fibrosis of basal segments, mid- segments and apical segments

Native T_1 mapping values (msec)	LGE						T- Test	
	+ve			-ve				
	Mean	±	SD	Mean	±	SD	T	P- value
Basal A	1054.231	±	38.257	1035.333	±	71.713	1.064	0.294

Basal AS	1065.346	±	48.889	1035.667	±	55.061	1.672	0.103
Basal IS	1066.538	±	51.309	1030.417	±	45.590	2.085	0.044*
Basal I	1067.038	±	62.730	1024.833	±	40.689	2.125	0.041*
Basal IL	1065.923	±	54.649	1027.917	±	72.725	1.793	0.081
Basal AL	1060.923	±	44.321	1034.167	±	60.541	1.538	0.133
Mid A	1061.192	±	46.885	1018.417	±	33.315	2.838	0.007*
Mid AS	1068.538	±	43.330	1033.500	±	48.641	2.230	0.032*
Mid IS	1066.115	±	42.535	1032.667	±	36.552	2.349	0.024*
Mid I	1059.192	±	36.087	1022.500	±	30.168	3.058	0.004*
Mid IL	1046.846	±	37.645	1008.667	±	27.773	3.132	0.003*
Mid AL	1039.577	±	34.077	1020.500	±	28.558	1.682	0.101
Apical A	1040.000	±	75.777	1011.667	±	61.670	1.131	0.265
Apical S	1068.885	±	37.482	1032.750	±	67.274	2.132	0.040*
Apical I	1067.423	±	46.485	1004.833	±	39.347	4.037	<0.001*
Apical L	1065.038	±	53.968	1018.083	±	36.079	2.735	0.010*
Apical Apex	1048.692	±	52.388	1056.917	±	79.447	-0.381	0.706

T= Student t-test
P- value: probability.
*: p- value (< 0.05) is significant.

Table 4: Comparison between HCM patients and controls according to ECV%.

ECV%	Group						T- Test	
	HCM patients			Controls				
	Mean	±	SD	Mean	±	SD	t	P- value
Basal A	28.132	±	4.199	22.800	±	2.044	3.873	<0.001*
Basal AS	30.263	±	4.196	24.600	±	1.838	4.139	<0.001*
Basal IS	29.211	±	4.127	24.800	±	2.150	3.247	0.002*
Basal I	29.763	±	5.405	25.200	±	1.814	2.613	0.012*
Basal IL	30.000	±	4.667	25.400	±	2.271	3.007	0.004*
Basal AL	29.237	±	5.673	24.000	±	1.155	2.881	0.006*
Mid A	28.842	±	5.893	24.000	±	2.000	2.542	0.014*
Mid AS	29.263	±	4.803	25.800	±	2.616	2.185	0.034*
Mid IS	28.684	±	4.731	23.600	±	1.955	3.303	0.002*
Mid I	28.711	±	7.443	23.800	±	2.044	2.051	0.046*
Mid IL	28.289	±	5.018	24.000	±	3.333	2.548	0.014*
Mid AL	27.763	±	4.239	24.600	±	2.547	2.245	0.030*
Apical A	31.263	±	7.689	27.200	±	1.814	1.647	0.106
Apical S	30.289	±	6.247	25.800	±	1.687	2.235	0.030*
Apical I	28.842	±	5.838	23.600	±	0.516	2.814	0.007*
Apical L	30.158	±	6.158	25.400	±	1.265	2.412	0.020*
Apex	30.395	±	5.504	27.400	±	0.843	1.702	0.096
Average	29.359	±	5.501	24.823	±	1.876	2.673	0.025*

T= Student t-test
P- value: probability.
*: p- value (< 0.05) is significant.

Table 5: Comparison between mean values of ECV% according to late contrast enhanced imaging for fibrosis of basal segments, mid-segments and apical segments.

ECV%	LGE						T- Test	
	+ve			-ve				
	Mean	±	SD	Mean	±	SD	t	P- value
Basal A	29.385	±	4.196	25.417	±	2.746	2.983	0.005*
Basal AS	31.192	±	4.552	28.250	±	2.379	2.100	0.043*
Basal IS	30.385	±	3.920	26.667	±	3.473	2.812	0.008*
Basal I	30.692	±	5.690	27.750	±	4.267	1.592	0.120
Basal IL	31.000	±	4.596	27.833	±	4.218	2.024	0.050*
Basal AL	30.115	±	6.244	27.333	±	3.725	1.425	0.163
Mid A	30.308	±	6.298	25.667	±	3.257	2.397	0.022*
Mid AS	30.885	±	4.693	25.750	±	2.800	3.498	0.001*
Mid IS	29.885	±	4.958	26.083	±	2.937	2.453	0.019*
Mid I	30.115	±	8.392	25.667	±	3.393	1.761	0.087
Mid IL	29.346	±	5.306	26.000	±	3.516	1.985	0.055
Mid AL	28.038	±	4.395	27.167	±	3.996	0.584	0.563
Apical A	32.538	±	8.320	28.500	±	5.419	1.532	0.134
Apical S	31.308	±	6.614	28.083	±	4.907	1.504	0.141
Apical I	29.462	±	6.243	27.500	±	4.815	0.962	0.343
Apical L	31.000	±	6.934	28.333	±	3.601	1.250	0.219
Apical Apex	30.846	±	6.038	29.417	±	4.188	0.740	0.464

T= Student t-test
P- value: probability.
*: p- value (< 0.05) is significant.

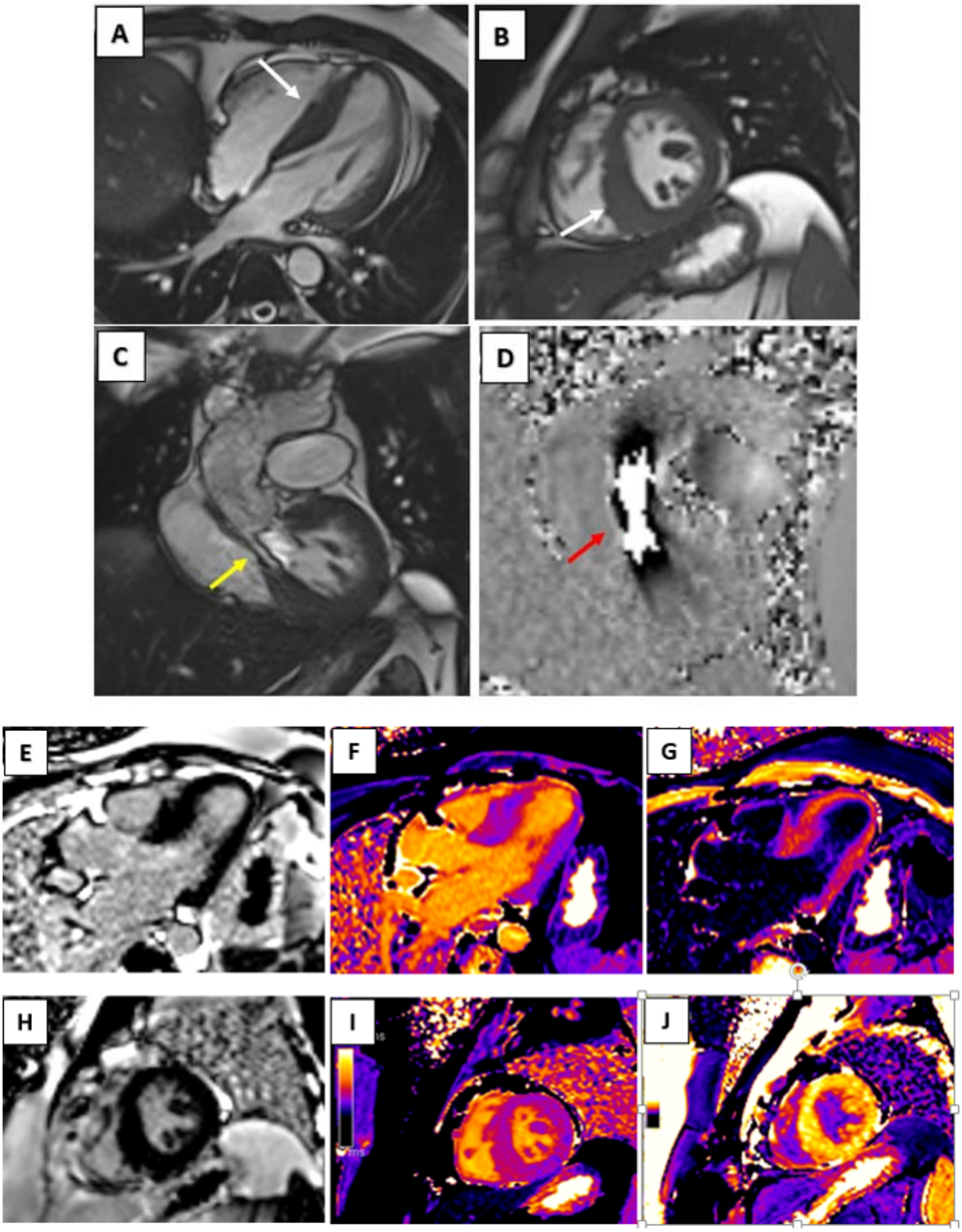

Fig 1: (A-J images): A 46-year-old male patient. He had one attack of compressing chest pain radiating to the left shoulder 2 months ago. (A) 4 chamber ED SSFP image and (B) SAX ED SSFP image showing asymmetrical LV septal hypertrophy involving mainly the basal and mid septal segments (white arrows). (C) LVOT SSFP cine image showing LVOT obstruction with dephacing jet (yellow arrow) associated with SAM, and (D) LVOT in-plane phase contrst image at 150 cm/sec showing aliasing (red arrow). (E& H) 3chamber and mid-ventricular SAX LGE images showing no intramyocardial enhancement/ fibrosis, (F& I) Precontrast T_1 mapping 3chamber & SAX images, and (G& J) Post contrast T_1 mapping images no color maps defects with increased T_1 mapping in basal and mid-ventricular septal segments and calculated ECV% was increased only at basal antro septal segment. The case was diagnose as hypertrophic obstructive cardiomyopathy with

no late gadolinium enhancement.

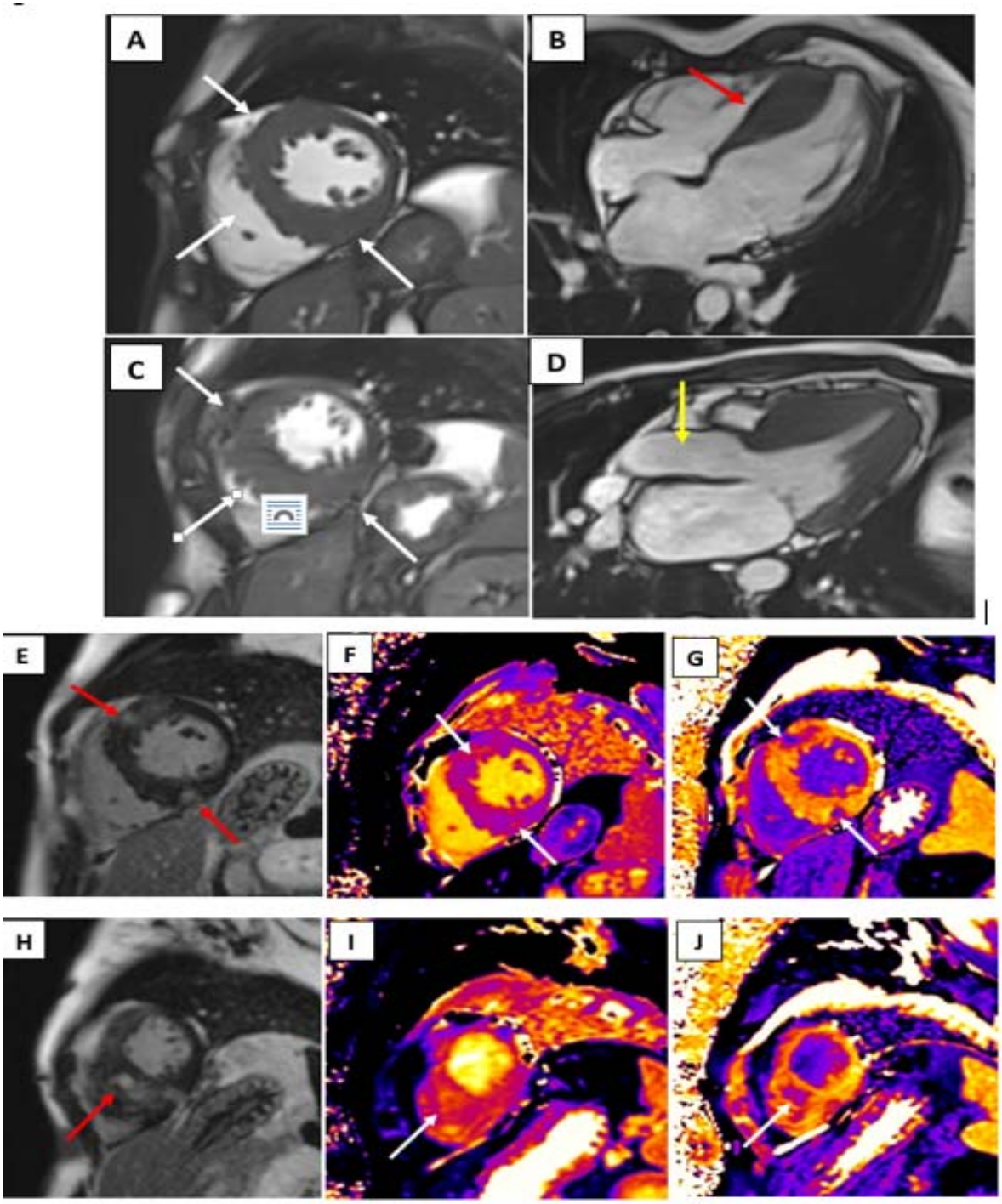

Fig 2: (A-J images): A 28-year-old male patient with palpitation, and had a previous history of syncopal attack 4 months ago. ECHO revealed left ventricle hypertrophy. (A) mid-ventricular SAX ED SSFP image, (B) 4 chamber ED SSFP image, and (C) apical SAX ED SSFP image showing asymmetrical anti-clock wise LV hypertrophy (white arrows) with maximum thickness seen at mid-ventricular septal segments (red arrow), and (D) 3 chamber ES SSFP cine image showing no LVOT obstruction nor SAM (yellow arrow). (E& H) Mid-ventricular and apical LGE SAX images showing multiple patches of focal intramyocardial fibrosis at mid anterior, antro-septal and inferior insertion points as well as extensvive apical anterior and septal fibrosis (red arrows), (F& I) Precontrast T_1 mapping SAX images, and (G& J) Post contrast T_1 mapping images showing color map defect at the same regions of LGE (white arrows) with increased T_1 mapping and increased calculated ECV%. The case was diagnosed as hypertrophic non obstructive cardiomyopathy with anti-clock wise pattern showing multi-focal areas of patchy enhnacement /fibrosis.

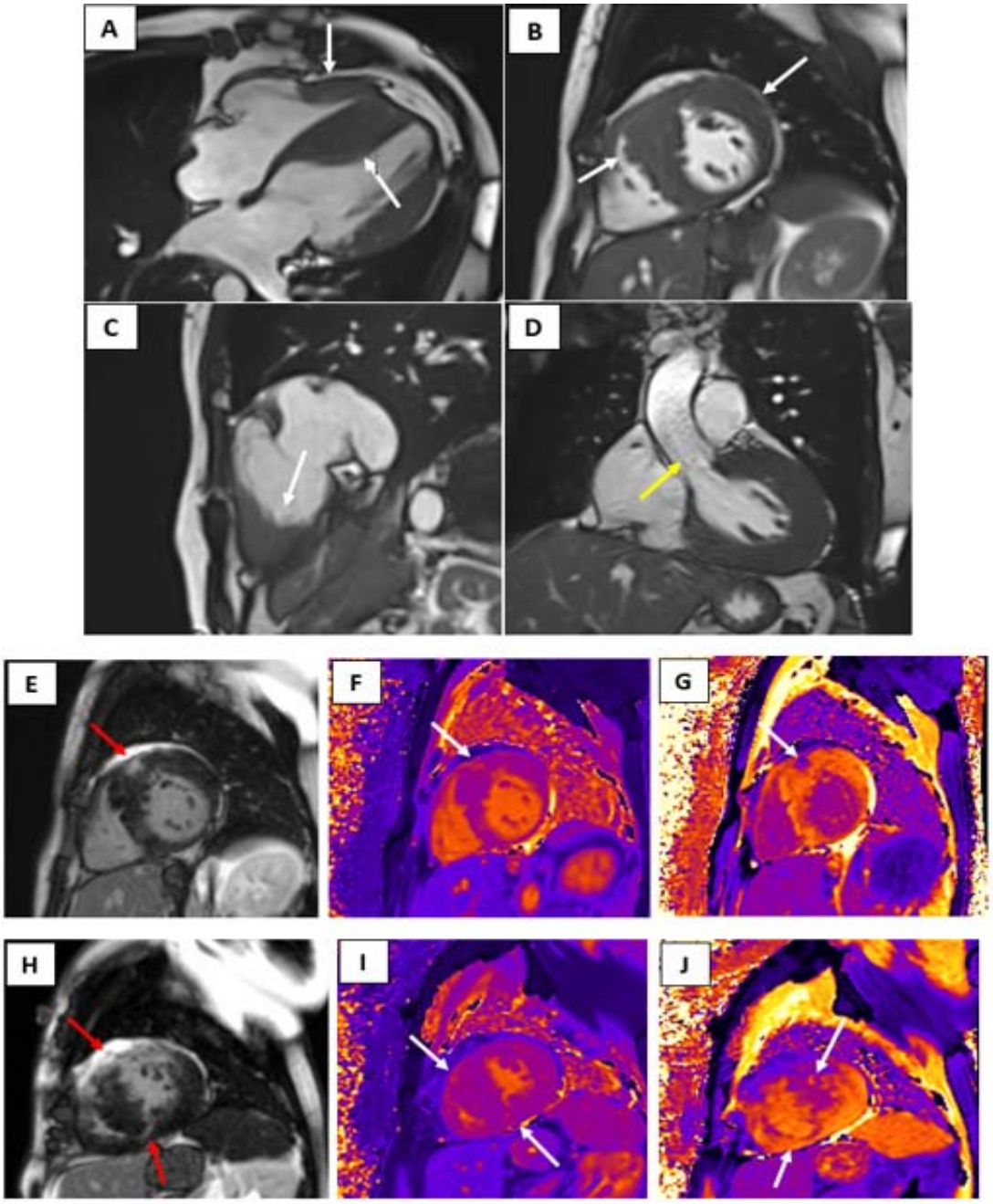

Fig 3: (A-J images): A 38-year-old female patient with dyspnea and palpitation for 2 years, and had become worse recently. ECHO showed asymmetrical septal hypertrophy and preserved LF function. (A) 4 chamber ED SSFP image and (B) SAX ED SSFP image (C) 2 chamber ED RV SSFP image showing biventricular hypertrophy involving mainly the interventricular septum and anterior segments (white arrows) with maximum thickness at mid antroseptal segment, and (D) LVOT SSFP image shows no evidence of LVOT obstruction (yellow arrow), no aliasing nor dephacing jet. (E& H) Basal and Mid-ventricular LGE SAX images showing focal intramyocardial fibrosis at basal anterior insertion point and focal transmural enhancement of mid anterior segment and true apex as well as patchy intramyocardial enhancement in mid infero-septal segment, (F& I) Precontrast basal and mid-ventricular SAX T_1 mapping images, and (G& J) Post contrast T_1 mapping basal and mid ventriculr SAX images showing color map defect at the same regions of LGE with increased T_1 mapping and calculated ECV% as well as other mid-ventricular and apical segments with no LGE. The case was diagnose as bi-ventricular hypertrophic cardiomyopathy with multi-focal areas of intramyocardial late gadolinium enhancement/fibrosis as well as mid and apical transmural fibrosis (ischemic) likley burnet out myocardium.

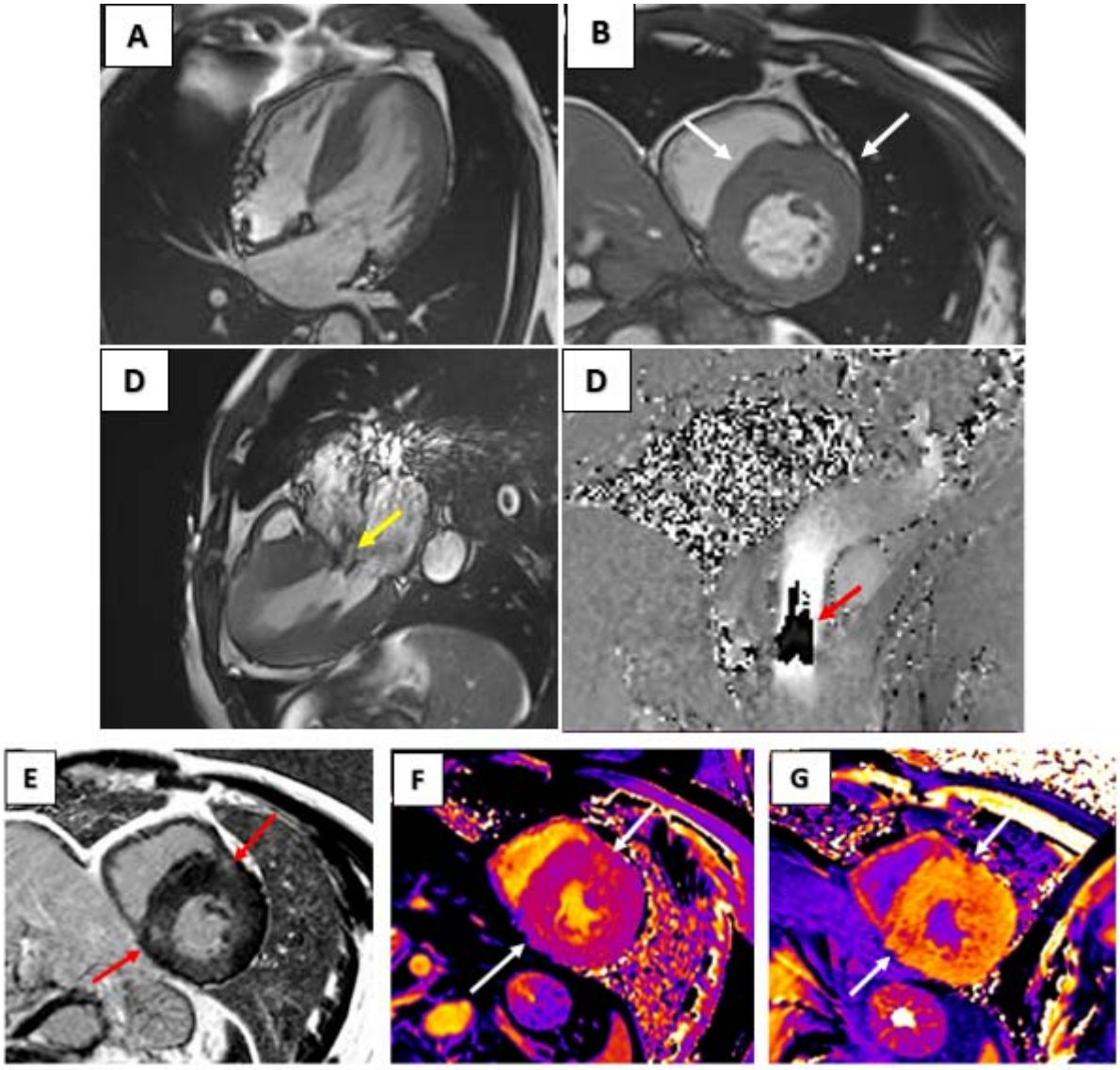

Fig 4: (A-G images): A 57-year-old male patient with palpitation for 10 years that had become worse recently. ECHO revealed non dilated left ventricle with septal hypertrophy and preservation of global contractility. (A) 4 chamber ED SSFP image and (B) SAX ED SSFP image showing asymmetrical LV hypertrophy involving mainly the basal anterior and antroseptal segments (white arrows) with maximum thickness at mid anterior segment, (C) 3 chamber ES SSFP cine image showing LVOT obstruction with dephacing jet associated with SAM (yellow arrow), (D) LVOT in-plane Q-flow at 150 cm/sec showing aliasing (red arrow), (E) Mid-ventricular LGE SAX image showing focal intramyocardial fibrosis at anterior and posterior insertion points (red arrows), (F) Precontrast T_1 mapping SAX image, and (G) Post contrast T_1 mapping image showing color map defect at the same regions of LGE (white arrows) with increased T_1 mapping and calculated ECV%. The case was diagnosed as hypertrophic obstructive cardiomyopathy with late gadolinium enhancement.

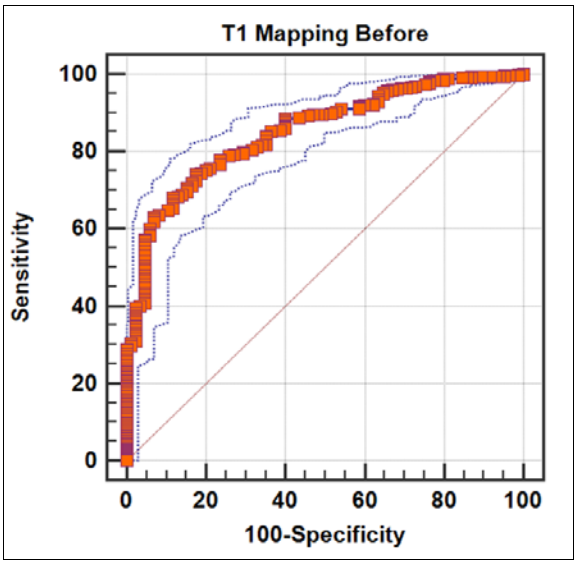

Fig 5: ROC-curve between HCM patients and controls according to native T_1 mapping.

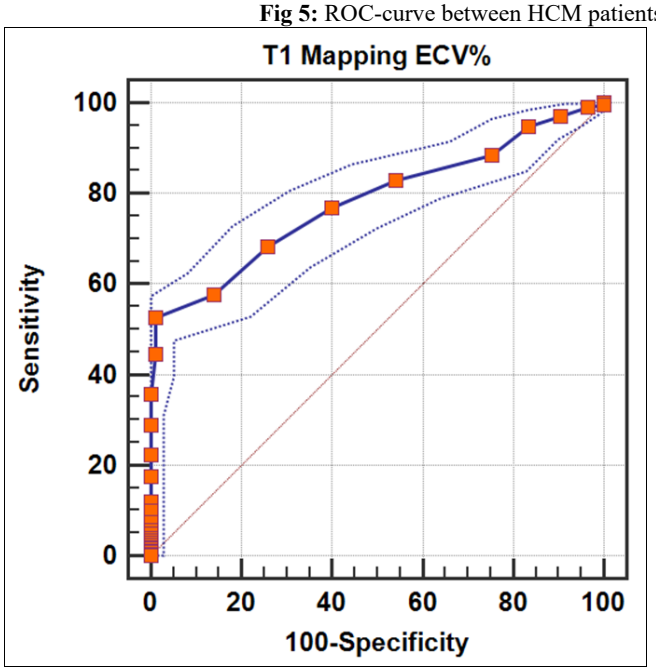

Fig 6: ROC-curve between HCM patients and controls according to ECV%

Discussion

This study aimed at comparing native cardiac T_1 and ECV fraction values within individuals having HCM and controls to value myocardial fibrosis in HCM even if not detected by LGE. Forty-eight cardiac MRI examinations were enrolled in our study for two groups; patients group involving 38 individuals having HCM and 10 healthy volunteers as controls.

In our study, 68.42% of the patients had patchy intra-myocardial late gadolinium enhancement denoting macroscopic fibrosis; the mid antero-septal segment was the most frequent site for fibrosis reported in 34.21% of them, out of them, 13% also demonstrated ischemic pattern of enhancement (subendocardial/transmural), while 31.58% showed no late gadolinium enhancement that agrees with Habib, *et al.* [9] who reported that 50% to 2/3 individuals having HCM developed varying levels of patchy mid wall myocardial fibrosis.

Late gadolinium enhancement could help detect individuals having HCM at high chances of SCD, thus defining if an ICD could be implanted [10]. Chan, *et al.* [11] addressed a linear correlation among LGE among and SCD risks in HCM patients, even after adjustment of other variables as age and LVEF.

Nowadays, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines depend on LGE as a moderator towards the decision for ICD implantation within individuals at high chances of developing abrupt cardiac death [9].

According to the enhanced ACC/AHA guidelines, individuals who have high chances of SCD were considered if they develop a primary risk factor of these involving: family history of SCD, unexplained syncope, maximal LVWT ≥30mm, NSVT, LGE/LV mass ≥15%, end-stage LV ejection fraction (LVEF) <50%, and LV apical aneurysm [12].

Myocardial T_1 mapping and ECV are non-invasive processe that measure pre and post-contrast myocardial and blood T_1 relaxation times to estimate diffuse myocardial fibrosis [13].

Due to high predominance of fibrosis in the inter-ventricular septum, special emphasis was placed on it in previous researches, but in our study, all segments were assessed to set the minimum average value of T_1 to reveal diffuse fibrosis.

We found the range of native T_1 from 917 msec to 1041 msec and the range of ECV values from 20% to 27% denoting a healthy myocardium without scarring, fibrosis or infiltration. T_1 mapping yielded images of excellent diagnostic quality. Neilan, *et al.* [14] found that the age of healthy controls affected the normal range of ECV with an average of 0.25 +- 0.02 in subjects whose ages are below 40 years as opposed to 0.32 +- 0.20 within individuals above 60 years.

The present study showed a significantly longer native T_1 and shorter post-contrast T_1 values within individuals having HCM as opposed to controls at all-time points (p<0.01) with significantly greater ECV within HCM ones as opposed to controls (p<0.02). Thongsongsang, *et al.* [15] addressed, native T_1 mapping had high diagnostic precision when differentiating myocardial disease and CAD from controls. Also, Gao, *et al.* [16] addressed significantly greater mean native myocardial T_1 and ECV in patients as opposed to controls (p≤0.001, respectively).

The meta-analysis of Minegishi, *et al.* [7] addressed a significantly longer mean native T_1 values within individuals having HCM (1019 ± 60 ms) as opposed to healthy controls (963 ± 41 ms) (p<0.001), and significantly greater ECVs (28 ± 4%) within individuals having HCM as opposed to healthy controls (27 ± 3%) (p<0.001).

Whereas Brouwer, *et al.* [17] addressed, there were no variations concerning ECV in non-enhanced myocardium when compared with controls.

Qin, *et al.* [18] addressed, T_1 mapping, particularly global native T_1 mapping with close follow up of the patients, could supply additional values complementary to the current guidelines in estimating major adverse cardiovascular events or sudden cardiac death and planning for advanced therapies.

As we reported significantly higher native T_1 values of individuals having LGE as opposed to others without LGE in 10 segments, Puntmann, *et al.* [19], and Dass, *et al.* [20] also addressed, T_1 mapping is effective when revealing myocardial alterations within individuals having HCM in addition to classic methods of measuring the thickness of myocardial wall and LGE with an increase of native T_1 values within HCM individuals as opposed to controls noticed in segments with and without LGE.

However, Iles, *et al.* [21] noticed no significant variation in myocardial T_1 native values in individuals suffering from HF, this might be attributed to variations in patient selection, imaging techniques and field strength utilized leading to different longitudinal relaxation measurements in native myocardium.

There was no significant elongation of T_1 measurements at some basal and apical segments noticed in our research due to inferior wall artifacts caused by typical susceptibilities artifacts and partial volumes effects demonstrated on T_1-mapping utilizing modified lock locker inversion recovinery technique, beside the diaphragmatic motion. So, wi further techniques are needed to assess the T_1-maps quality and strength.

Our study addressed, ECV in HCM individuals with LGE

were significantly greater as opposed to patients without LGE in 7 segments. This result agrees with a study carried out by Ho [22] on 88 individuals (37 G+/LVH+ overt HCM subjects, 29 G+/LVH− subjects, 11 normal controls, and 11 sarcomere-negative HCM subjects) who approved that myocardial ECV were high in HCM sarcomere mutation carriers even in the LVH absence(0.33±0.01 in G+/LVH−) and (0.36±0.01in G+/LVH+). This supports that fibrotic remodeling is aroused early in disease pathogenesis and subclinical myocardial anomalies may outrun HCM progression within gene-positive patients, so calculating ECV may help in characterization of myocardial fibrosis in HCM, thus helping introduce novel therapy specific for interstitial fibrosis.

Another study carried out by Ellims, *et al.* [23] on 76 patients (51HCM patients having [asymmetric septal hypertrophy and 25 healthy controls) revealed significantly shorter post-contrast myocardial T_1 time in HCM individuals as opposed to controls (498 ± 80 ms vs. 561 ± 47 ms, $p<0.001$) denoting diffuse myocardial fibrosis.

Regarding to those, a T_1 threshold of 1066 ms can distinguishes between segments with fibrosis and normal segments, based on ROC analysis of all segments, with a sensitivity of 74%, a specificity of 82%, with accuracy of 85% for myocardial fibrosis detection, and ECV% of 28%, is the most appropriate threshold to assess fibrosis with a sensitivity of 53%, a specificity of 98%, and an accuracy of 78% for myocardial fibrosis identification.

Recently, T_1 mapping images of mytocardium in histological analysis can be used to extract novel reproducible imaging markers characterizing disease-specific patterns of fibrosis and thus identifying various cardiomyopathies [24].

Study Limitations

The modest number of selected participants, represents the main limitation. Also, the described thresholds cannot be applied at other institutions as myocardial native T_1 values and ECV% depend to some degree on scanner and sequence. Unfortunately, the software used to quantify the scar burden was no available in our institute. Additionally, this research lacks direct histopathological confirmation which proves the correspondence of native T_1 values having actual myocardial fibrosis, and the relation to the prognosis.

Conclusions

From this study, we concluded that the estimate of native T_1 values and ECVs is beneficial while detection and quantification of diffuse interstitial myocardial fibrosis lost on LGE-MRI sequence that is a primary cause of diastolic dysfunction, heart failure, and SCD in HCM patients without necessity for administration of intravenous contrast material particularly in individuals having end-stage chronic kidney disorders or allergic reactions.

More research is required to apply such findings in clinical use. We also recommended prolonged follow-ups for HCM individuals to assess disease progression that may help in setting ideal treatments, thus decreasing arrhythmias and HF risks in those patients.

List of abbreviations

Anterior (A), antero-lateral (AL), antero-septal (AS), cardiovascular Magnetic Resonance (CMR), ejection fraction (EF), electrocardiogram (ECG), end-diastolic volume (EDV), end-diastolic volume indexed (EDVI), end-systolic volumes (ESV), end-systolic volume indexed (EDVI), extracellular volume fraction (ECV), hematocrit (Hct), hypertrophic cardiomyopathy (HCM), Inferior (I), infero-lateral (IL), infero-septal (IS), late gadolinium enhancement magnetic resonance imaging (LGE-MRI), lateral (L), left ventricle (LV), left ventricular outflow tract (LVOT) planes, modified look-locker Inversion recovery (MOLLI), right ventricle (RV), septal (S), short axis (SAX), steady state free precession (SSFP), sudden cardiac death (SCD), stroke volume (SV), stroke volume indexed (SVI), systolic anterior motion (SAM), velocity encoding (Venc).

Acknowledgements

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Declarations

1. Ethics approval and consent to participate

- Informed written consents taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta university hospital, faculty of medicine.
- Committee's reference number: 34029/08/20.

2. Consent for publication: All participants included in the research gave written consent to publish the data included in the study.

3. Availability of data and material: The author's confirm that all data supporting the finding of the study are available within the article and the raw data ad data supporting the findings were generated and available at the corresponding author on request.

4. Competing interests: The authors declare that they have no competing of interests.

5. Funding: No funding was obtained for this study.

6. Authors' contributions

- All authors read and approved the final manuscript for submission
- KI suggested the research idea, MA ensured the original figures and data in the work, minimized the obstacles to the team of work, IM correlated the study concept and design and had the major role in analysis, FE collected data in all stages of manuscript, performed data analysis. HA supervised the study with significant contribution to design the methodology, manuscript revision and preparation. MR correlated the clinical data of patient and matched it with the findings, drafted and revised the work.

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