Myocardial Triglyceride Content and Late Gadolinium Enhancement in Hypertrophic Cardiomyopathy with Asymmetric Septal Hypertrophy

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Abstract

Asymmetric septal hypertrophy (ASH) is the most common phenotype of hypertrophic cardiomyopathy (HCM). However, the difference between myocardial metabolism and myocardial features such as myocardial fibrosis and myofiber disarray in HCM remains unclear.

Cardiac magnetic resonance (CMR) and proton magnetic resonance spectroscopy (^{1}H-MRS) were performed on 16 patients diagnosed as HCM with ASH to assess the differences in myocardial features and morphology.

There were 7 patients who had LGE in ASH localized with the voxel of ^{1}H-MRS. The LV ejection fraction was significantly lower in the LGE (+) group than in the LGE (−) group (64.8% ± 4.9% vs. 72.1% ± 3.8%, P = 0.004). LV end-systolic volume was significantly greater in the LGE (+) group than in the LGE (−) group (51 ± 11 ml vs. 33 ± 12 ml, P = 0.007). A significant difference in MTG content was observed between patients in the LGE (+) group and in the LGE (−) group (0.58% ± 0.22% vs 1.29% ± 0.73%, P = 0.03). MTG content was significantly associated with LV ejection fraction, LV end systolic volume, and LV mass. In multivariate analyses, LV ejection fraction had an independent association with MTG content (P = 0.01)

Our data suggest that the metabolism of the septum in HCM with ASH may be different based on the absence or presence of LGE and that measurement of MTG content by ^{1}H-MRS may be useful to evaluate the characteristics of myocardial metabolic changes caused by the LV remodeling process in HCM.

(248 words)

Introduction

Hypertrophic cardiomyopathy (HCM) is a diverse clinical and pathophysiologic entity that mainly involves the left ventricle [1]. The causal genetic mutations of HCM are varied, but HCM can be classified into several phenotypes [2]. Asymmetric septal hypertrophy (ASH) is the most common phenotype of HCM. The phenotypes of HCM are directly related to clinical symptoms, left ventricular (LV) outflow obstruction, ventricular tachyarrhythmia, and myocardial fibrosis [3, 4]. Myocardial disarray or disorganization is considered as one of the features of ASH. However, the difference between myocardial metabolism and myocardial features such as myocardial fibrosis and myofiber disarray in HCM remain unclear.

Cardiac magnetic resonance (CMR) has a well-established role in the diagnostic assessment and risk stratification of cardiomyopathy and is a noninvasive method of assessing LV function and LV mass, which have been shown to be predictors of adverse outcomes in patients with HCM [5, 6]. Late gadolinium enhancement (LGE), T1 mapping and T2-weighted images provide additional information on regional increases in myocardial fibrosis, the risk of ventricular arrhythmia, and poor prognosis in patients with HCM [7, 8]. Furthermore, proton magnetic resonance spectroscopy (^{1}H-MRS) enables noninvasive measurement of myocardial triglyceride (MTG) content, which is reported to be associated with metabolic disorders, cardiac hemodynamics, and LV systolic and diastolic dysfunction [9–11]. However, there are

only a few reports on the MTG content in patients with HCM [12, 13]. In addition, the role of MTG content in patients with HCM has not been fully investigated.

The aims of this study were to compare MTG content assessed by ^{1}H-MRS in patients diagnosed as HCM with ASH and to evaluate the associations among MTG content, cardiac morphology, cardiac function and myocardial features.

Materials And Methods

Subjects

We enrolled 36 consecutive patients diagnosed with HCM according to the guideline of the European Society of Cardiology [14]. HCM is defined by a wall thickness of 15 mm or more in one or more LV myocardial segments as measured by ultrasonic echocardiography (UCG). In cases with lesser amounts of wall thickening (13–14 mm), the diagnosis of HCM requires evaluation of other features, including family history, noncardiac symptoms and signs, electrocardiographic abnormalities, and laboratory tests. HCM was diagnosed on the basis of typical clinical, echocardiographic, and hemodynamic features, according to established criteria [15, 16]. Four patients were excluded because LGE images could not performed due to severe chronic kidney disease. Sixteen patients had ASH. ASH was defined as ≥ 1.3 of the echocardiographic interventricular septum to LV free wall thickness ratio [17].

The ethical committee of Juntendo University approved the study protocol developed in accordance with the principles established in the Declaration of Helsinki, and all patients provided written informed consent before participating in this study.

Blood measurements

Standard laboratory tests including blood cell count, biochemical markers, lipid profile markers, blood sugar, serum creatinine, urinary acid, brain natriuretic peptide (BNP), and glycosylated hemoglobin (HbA1c), were performed.

Magnetic resonance imaging and magnetic resonance spectroscopy

All CMR and ^{1}H-MRS studies were conducted with a MAGNETOM Avanto 1.5-T MRI system (Siemens Medical Solution, Erlangen, Germany) with the subjects resting in the supine position. To minimize the influence of breathing, a towel was strapped around the subject's upper abdomen. Dynamic cine images were used to determine LV mass and LV functional parameters. Image analysis was conducted with special evaluation software (Argus; Siemens Medical Systems, Erlangen, Germany) on a separate work station [18, 19]. Endocardial and epicardial LV borders were traced manually at end-diastole and end-systole from short-axis cine images. End-diastolic volume, end-systolic volume, stroke volume and ejection fraction were calculated by Simpson's method. In addition, the peak LV ejection and filling rates were automatically derived based on LV volume–time curves.

After cine images, MTG content was determined by ^{1}H-MRS. In brief, a volume of interest (VOI = 2.0 cm^3 – 10 × 10 × 20 mm) was selected within the ventricular septum from cine dynamic cine-mode images of the heart (Fig. 1-A). We determined the VOI size to fit the septum of the left ventricle anatomically. The spectrum of water and lipid was acquired by point-resolved spectroscopy method, which used a section-selective 90° pulse, followed by two section-selective refocusing pulses using spin echo with an echo time of 30 msec and a repetition time of at least 4000 msec. MTG signals were acquired at 1.4 ppm from spectra with water suppression, and water signals were acquired at 4.7 ppm from spectra without water suppression (Fig. 1); a total of 64 signals were acquired. Areas under the curve for water and lipid peaks were quantified using standard line-fitting procedures (Siemens Syngo Spectroscopy). The MTG level was expressed as the ratio of lipid to water (%). ^{1}H-MRS evaluation of MTG content was performed essentially as previously described [13, 20, 21].

Finally, LGE was assessed at least 10 min after intravenous administration of 0.1 mmol/kg body weight of a gadolinium-based contrast agent (Magnevist, Bayer Health Care, Berlin Germany, or ProHance, Bracco, Milan, Italy) in a short-axis section using an inversion recovery gradient echo sequence (slice thickness of 8 mm, no gap). The inversion time was manually adjusted using inversion time scout (range, 170–320 msec) to null the signal from the normal myocardium as recommend by the protocol of the Society of Cardiovascular Magnetic Resonance [22].

Statistical analysis

Values are expressed as means ± standard deviation. For variables that did not show a normal distribution, the data were transformed into natural logarithmic values before statistical analysis. Correlations were calculated using Pearson's correlation coefficient. The unpaired Student's *t* test was used to compare groups. We performed multivariable linear regression analysis to assess determinants of the MTG content. All statistical analyses were performed using the SPSS version 20 software package (SPSS, Chicago, Illinois). A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

There were 7 patients who had LGE in ASH localized with the voxel of ^{1}H-MRS (Fig. 1-B). The clinical characteristics of the study subjects, who were divided into two groups, the LGE (+) group and the LGE (−) group, are summarized in Table 1. The mean age was 58.0 ± 13.4 years, the mean body mass index (BMI) was 24.1 ± 5.0 kg/m^2 and the mean BNP was 167 ± 1147 ng/L. Three patients had been treated for diabetes mellitus. There were no significant differences between the LGE (+) group and the LGE (−) group.

Table 1
Clinical characteristics of study subjects

	Total (n = 16)	LGE (+) (n = 7)	LGE (−) (n = 9)	
Age, years	58.0 ± 13.4	52.0 ± 13.9	62.8 ± 11.5	0.11
Male gender, (%)	10 (63)	6 (85)	4 (44)	0.08
Body mass index, kg/m^2	24.1 ± 5.0	25.9 ± 6.0	22.5 ± 3.6	0.20
Diabetes mellitus, (%)	3 (19)	3 (43)	0 (0)	0.06
Total cholesterol, mg/dl	195 ± 17	195 ± 14	195 ± 23	0.94
Triglyceride, mg/dl	116 ± 50	128 ± 64	109 ± 42	0.52
LDL-cholesterol, mg/dl	117 ± 19	121 ± 22	114 ± 18	0.52
HDL-cholesterol, mg/dl	53 ± 10	48 ± 10	56 ± 10	0.25
Fasting blood glucose, mg/dl	106 ± 26	119 ± 34	95 ± 10	0.06
HbA1c, %	5.8 ± 0.6	6.1 ± 0.8	5.6 ± 0.5	0.20
AST, IU/L	27 ± 13	33 ± 15	22 ± 9	0.08
ALT, IU/L	25 ± 18	34 ± 24	17 ± 9	0.06
BUN, mg/dl	16.4 ± 3.1	16.0 ± 4.1	16.8 ± 2.2	0.63
Creatinine, mg/dl	0.80 ± 0.23	0.83 ± 0.20	0.78 ± 0.26	0.66
eGFR, mL/min/m^2	76 ± 19	82 ± 24	71 ± 15	0.25
Urinary acid, mg/L	5.8 ± 1.2	6.0 ± 1.1	5.7 ± 1.3	0.59
BNP, ng/L	167 ± 147	115 ± 75	219 ± 187	0.19
Values are mean ± SD.				
LGE, late gadolinium enhancement; ASH, asymmetric septal hypertrophy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.				

The UCG variables are shown in Table 2. The LV ejection fraction was significantly lower in the LGE (+) group than in the LGE (−) group (69% ± 4% vs. 74 ± 5%, P = 0.04). The LV end-systolic diameter was significantly greater in the LGE (+) group than in the LGE (−) group (28.1 ± 4.8 mm vs. 23.6 ± 2.8 mm, P = 0.03). There were no significant differences between groups in the other UCG variables.

Table 2
UCG variables

	Total (n = 16)	LGE (+) (n = 7)	LGE (−) (n = 9)	P
LV ejection fraction, %	71 ± 5	69 ± 4	74 ± 5	0.04
LV end-diastolic diameter, mm	43.4 ± 5.5	45.7 ± 7.0	41.7 ± 3.5	0.15
LV end-systolic diameter, mm	25.6 ± 4.4	28.1 ± 4.8	23.6 ± 2.8	0.03
IVS, mm	17 ± 4	17.7 ± 2.1	16.8 ± 4.5	0.62
PWT, mm	10.3 ± 1.5	10.9 ± 1.6	9.9 ± 1.4	0.20
Left atrial dimension, mm	39.2 ± 6.7	42.4 ± 4.7	36.7 ± 7.2	0.08
E/*A*	0.96 ± 0.36	0.86 ± 0.21	1.05 ± 0.45	0.31
Deceleration time, msec	242 ± 81	261 ± 67	228 ± 92	0.43
e', m/s	4.9 ± 1.0	4.5 ± 1.2	5.1 ± 0.9	0.24
E/*e*'	14.5 ± 5.8	14.5 ± 7.5	14.5 ± 4.7	0.99
Values are mean ± SD.				
UCG, ultrasound cardiogram; LGE, late gadolinium enhancement; LV, left ventricular; IVS, interventricular septum; PWT, posterior wall thickness; *E*/*A*, peak early diastolic LV filling velocity/peak atrial filling velocity ratio; *e*', peak early diastolic velocity of the annulus; *E*/*e*', peak early diastolic LV filling velocity/ peak early diastolic velocity of the annulus ratio.				

The MRI and MRS variables are shown in Table 3. The LV ejection fraction was significantly lower in the LGE (+) group than in the LGE (−) group (64.8% ± 4.9% vs. 72.1% ± 3.8%, $P = 0.004$); the same result was shown for the UCG variables. The LV end-systolic volume was significantly greater in the LGE (+) group than in the LGE (−) group (51 ± 11 mL vs. 33 ± 12 mL, $P = 0.007$). There were no significant differences between groups in the other MRI variables.

Table 3
MRI variables of study subjects

	Total (n = 16)	LGE (+) (n = 7)	LGE (−) (n = 9)	P
LV ejection fraction, %	68.9 ± 5.6	64.8 ± 4.9	72.1 ± 3.8	0.004
LV end diastolic volume, mL	130 ± 38	145 ± 30	118 ± 42	0.17
LV end systolic volume, mL	41 ± 14	51 ± 11	33 ± 12	0.007
Stroke volume, mL	89 ± 27	94 ± 22	85 ± 31	0.53
Cardiac output, L/min	5.7 ± 1.5	6.0 ± 1.4	5.4 ± 1.6	0.50
LV myocardial mass, g	172 ± 63	196 ± 46	154 ± 71	0.20
Peak ejection rate, mL/s	679 ± 346	725 ± 420	638 ± 290	0.64
Peak filling rate, mL/s	595 ± 285	679 ± 323	532 ± 256	0.35
Values are mean ± SD.				
MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; LV, left ventricular.				

The MTG content of the two groups are shown in Fig. 2. The MTG was significantly higher in the LGE (−) group than in the LGE (+) group (1.29% ± 0.73% vs 0.58% ± 0.3%., $P = 0.03$.

The correlations between MTG content and other parameters are shown in Table 4. In all patients, the MTG content was significantly associated with LV ejection fraction ($r = 0.54$, $P = 0.03$), LV end-diastolic volume ($r = -0.48$, $P = 0.05$), LV end-systolic volume ($r = -0.62$, $P = 0.01$), and LV mass ($r = -0.53$, $P = 0.03$). In the LGE (+) group, there were no significant correlations between MTG content and other parameters. In the LGE (−) group, MTG content was significantly associated with LV end-systolic volume ($r = -0.62$, $P = 0.01$), fasting blood sugar ($r = 0.71$, $P = 0.03$), and HbA1c ($r = 0.83$, $P = 0.02$).

Table 4
Correlations between myocardial TG content and cardiac functional parameters in LGE group and Non-LGE group

	All patients (n = 16)		LGE (+) (n = 7)		LGE (−) (n = 9)	
	r	*P*	*r*	*P*	*r*	*P*
Age	0.21	0.44	−0.42	0.35	0.13	0.74
BMI	0.003	0.99	0.22	0.63	0.30	0.47
LV ejection fraction	0.54	0.03	−0.10	0.83	0.50	0.17
LV end-diastolic volume	−0.48	0.05	0.49	0.26	−0.58	0.09
LV end-systolic volume	−0.62	0.01	0.51	0.24	−0.72	0.02
Stroke volume	−0.36	0.16	0.42	0.34	−0.51	0.16
Cardiac output	−0.22	0.42	0.53	0.22	−0.42	0.29
LV mass volume	−0.53	0.03	−0.28	0.55	−0.48	0.18
Peak ejection rate	−0.04	0.88	0.50	0.25	−0.27	0.52
Peak filling rate	−0.16	0.58	0.16	0.43	−0.25	0.54
IVS	−0.31	0.23	0.17	0.72	−0.36	0.34
PW	−0.30	0.25	−0.005	0.99	−0.23	0.54
E/*A*	0.32	0.24	−0.11	0.82	0.26	0.53
e'	0.13	0.25	0.73	0.06	−0.39	0.29
E/*e*'	0.08	0.63	−0.39	0.38	0.35	0.36
Triglyceride	0.12	0.69	−0.42	0.48	0.11	0.80
LDL-cholesterol	−0.18	0.57	0.12	0.84	−0.14	0.77
HDL-cholesterol	0.16	0.60	0.18	0.76	−0.09	0.83
Fating blood sugar	−0.003	0.99	0.36	0.43	0.71	0.03
HbA1c	0.22	0.49	0.74	0.15	0.83	0.02
AST	−0.004	0.98	0.57	0.10	0.02	0.96

LGE, late gadolinium enhancement; BMI, body mass index; LV, left ventricular; IVS, interventricular septum; PWT, posterior wall thickness; *E*/*A*, peak early diastolic LV filling velocity/peak atrial filling velocity ratio; *e*', peak early diastolic velocity of the annulus; *E*/*e*', peak early diastolic LV filling velocity/ peak early diastolic velocity of the annulus ratio; ; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; AST, aspartate transaminase; ALT, alanine transaminase; BNP, brain natriuretic peptide.

	All patients (n = 16)		LGE (+) (n = 7)		LGE (−) (n = 9)	
	r	*P*	*r*	*P*	*r*	*P*
ALT	−0.11	0.69	−0.62	0.13	0.50	0.16
Creatinine	−0.35	0.18	−0.57	0.18	−0.30	0.43
BNP	0.46	0.09	−0.03	0.89	0.47	0.28

LGE, late gadolinium enhancement; BMI, body mass index; LV, left ventricular; IVS, interventricular septum; PWT, posterior wall thickness; *E*/*A*, peak early diastolic LV filling velocity/peak atrial filling velocity ratio; *e*', peak early diastolic velocity of the annulus; *E*/*e*', peak early diastolic LV filling velocity/ peak early diastolic velocity of the annulus ratio; ; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; AST, aspartate transaminase; ALT, alanine transaminase; BNP, brain natriuretic peptide.

Multivariate analyses were performed on data pertaining to male gender, LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, LV mass and presence of diabetes mellitus. In this model, LV ejection fraction had an independent association with MTG content (Table 5).

Table 5
Multivariate logistic regression analysis for myocardial TG content

Factors	Univariate		Multivariate	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	0.97 (0.93 – 1.06)	0.11		
Male gender	2.50 (0.82 – 7.64)	0.09	0.58 (0.08 – 3.93)	0.58
History of DM	2.67 (0.67 – 10.5)	0.16		
Fasting blood glucose	0.99 (0.97 – 1.01)	0.99		
AST	1.01 (0.96 – 1.05)	0.65		
ALT	1.01 (0.97 – 1.04)	0.38		
Left atrial dimension	1.07 (0.98 – 1.18)	0.12		
LV ejection fraction	0.88 (0.78 – 0.97)	0.01	0.44 (0.23 – 0.82)	0.01
LV end-diastolic volume	1.01 (1.00 – 1.02)	0.04	1.17 (1.00 – 0.85)	0.06
LV end-systolic volume	1.05 (1.01 – 1.10)	0.01	0.54 (0.29 – 0.95)	0.05
LV mass volume	1.01 (1.00 – 1.02)	0.01	1.01 (0.99 – 1.04)	0.06
BNP	0.99 (0.99 – 1.00)	0.10		
Presence of LGE	4.60 (1.31 – 16.1)	0.01	8.12 (0.44 – 148)	0.15

DM, diabetes mellitus; AST, aspartate transaminase; ALT, alanine transaminase; LV, left ventricular; BNP, brain natriuretic peptide; LGE, late gadolinium enhancement.

Discussion

We demonstrated that MTG content was significantly higher in the LGE (−) group than in the LGE (+) group. In addition, MTG content was associated with LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, and LV mass. In multivariate analysis, LV ejection fraction had an independent association with MTG content. There are no reports of MRS performed on sites with delayed contrast images.

The LGE (−) group had a higher MTG content than the LGE (+) group. MTG has been reported to be associated with aging and metabolic disorders that increase free fatty acids, such as obesity, diabetes mellitus and fatty liver [9, 23–25]. The triglyceride pool was reactively enlarged under a high concentration of fatty acid in the myocardium to absorb the excess fatty acid and avoid cardiotoxicity [26]. In our data, although there is no significant difference between the two groups, the LGE (+) group had higher BMI, more patients with diabetes mellitus and a higher level of transaminases suggesting fatty liver. These factors suggesting metabolic abnormalities inherently increase MTG in the LGE (+)

group. On the other hand, the LGE (−) group tended to be older, and MTG is increased by aging. However, even considering there factors, these may be a metabolic abnormality specific to HCM that is responsible for the higher MTG in the LGE (−) group.

Thickened septum is thought to contain abnormal myocardium. Visual loss of midline cricothyroid muscle structure has been reported in the ventricular septum of subjects with HCM, especially in cases of asymmetric septal thickening. Therefore, the septum of subjects with HCM with ASH is thought to contain a complex arrangement of abnormal myocardium [27]. Although LGE is thought to be consistent with myocardial fibrosis, the LGE in the ventricular septum is thought to be an increase in interstitium due to the complex arrangement. In our method, MTG is calculated by dividing the signal of the fat component by the signal of the water component. If there is more extracellular fluid, MTG will inevitably decrease. Another possibility is that because LGE reflects fibrosis of the myocardium, MTG will inevitably decrease in fibrotic myocardium if the fibroblast is already in an energy-depleted state.

Another possibility is that the metabolism of cardiomyocytes is different in abnormal myocardium compared with normal myocardium. A decrease in intracellular creatine has been reported to be observed in HCM from the beginning of the disease [28]. Because adenosine diphosphate (ADP) is originally transformed into adenosine triphosphate (ATP) using creatine as a catalyst, a decrease in creatine causes an increase in intracellular ADP and an increase in Ca^{2+} concentration [29]. High ADP levels reported to impair relaxation of hearts via ADP-mediated defects in sarcomere function in an animal study [30], and ADP increased myofilament Ca^{2+} sensitivity in HCM patients [31]. Increased binding of Ca^{2+} to the myofilaments by way of increased Ca^{2+} sensitivity will reduce Krebs cycle activity. Consequently, impaired sarcomere energetics may thus provoke mitochondrial dysfunction, which may increase MTG by reducing the efficiency of fatty acid oxidation. These findings suggest that MTG tends to accumulate from the early stage of the disease and may decrease as the disease progress.

MTG significantly related to morphologic parameters, such as LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, and LV mass. Several studies have reported a positive correlation between MTG and LV mass in patients with diabetes mellitus, and obesity, and increased LV mass was accompanied by both increased LV concentricity and a subtle decrease in regional systolic performance. In addition, there are similar reports that increased MTG content leads to disturbance of LV systolic and diastolic functions [9, 11, 24]. In contrast, we have previously shown that MTG is negatively correlated with LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, and LV mass in athletes and healthy subjects [20]. These differences suggest that the implications of MTG differ between cardiomyopathy and normal myocardium. Especially in HCM, sarcomere energetics is impaired due to genetic predisposition as described above, and myocardial metabolism is thought to be very different. Further research focusing on myocardial metabolism is required.

Limitations

First, this study had a small sample size and was conducted at a single centre. Second, we have no data on the results of genetic analysis and did not performed biopsies of the myocardium for all subjects. Third, duration of each disease could not be ascertained. Moreover, some patients had already received medical treatment, including inhibitors of the renin–angiotensin aldosterone system or β-blockers. The effects of these treatments on myocardial metabolism need to be investigated. Finally, the parameters assessed by ^{1}H-MRS have not been revealed fully. More studies with ^{1}H-MRS are recommended in the future.

Conclusions

This study demonstrated that MTG was different in patients diagnosed as HCM with ASH based on the absence or presence of LGE. This indicated that measurement of MTG content by ^{1}H-MRS may be useful to evaluate the characteristics of myocardial metabolic changes caused by the LV remodeling process in HCM.

Declarations

Conflict of interest

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Figures

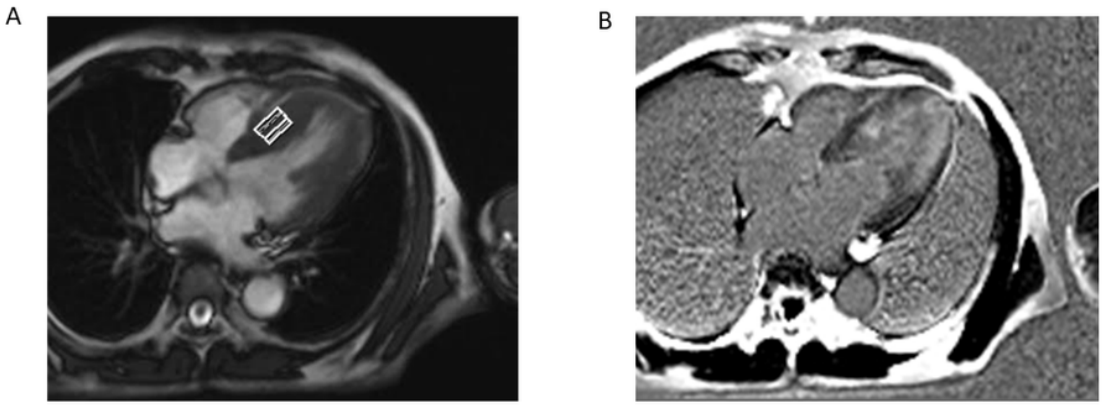

Figure 1

Representative images of patients with HCM.

(A) Myocardial voxel localisation for H^1-MRS in four-chamber. (B) Late gadolinium enhancement in septum including voxel localisation.

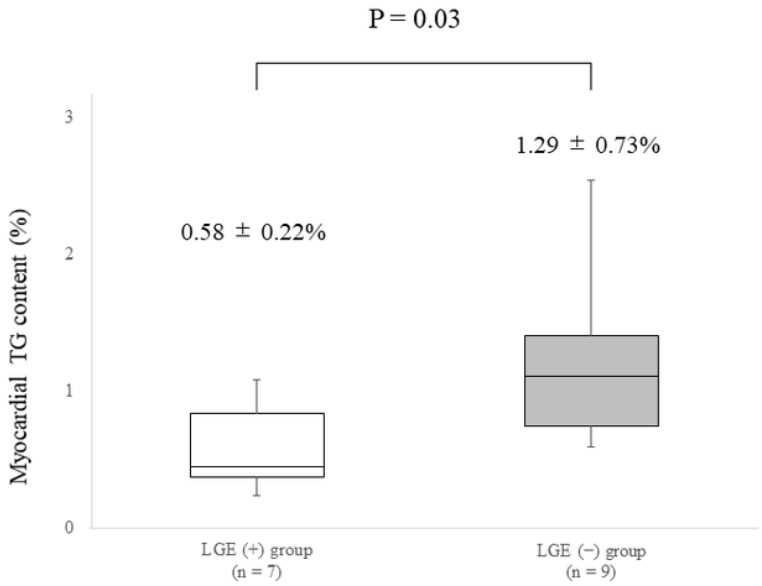

Figure 2

Comparison between myocardial TG content in the LGE group and the Non-LGE group.