Use of Serum Creatine Kinase MM Isoforms for Predicting the Progression of Left Ventricular Dilation in Patients With Hypertrophic Cardiomyopathy

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Serum creatine kinase (CK) isoforms were examined to detect the progression of left ventricular (LV) enlargement with reduced motion, resembling dilated cardiomyopathy (DCM), in hypertrophic cardiomyopathy (HCM). Changes in LV indices were determined annually by echocardiography in 51 patients until serum measurements (first follow-up period, 6.5 ± 2.2 years). Serum creatine isoforms (CKMM1, CKMM2 and CKMM3) were measured with high-voltage electrophoresis in 35 of these patients from 1991 to 1992, and the data for these latter patients are reported here. Serum total CK, CKMB, lactate dehydrogenase and its isoenzyme LDH1 were also measured. The changes in LV indices were further monitored until January, 1995 (second follow-up). During the 2 follow-up periods, the patients in the on-going group showed a reduction in the LV ejection fraction (LVEF) to $<55\%$ with LV end-diastolic dimension (LVDd) <55 mm, and those in the DCM-like group showed a reduction in LVEF to $<55\%$ and an increase in LVDd to ≥ 55 mm. During the first follow-up period, LVEF and LVDd remained at $\geq 55\%$ and <55 mm, respectively, in 26 patients (nonprogressive-disease group), while 3 patients entered the on-going group and 6 entered the DCM-like group. The CKMM3/CKMM1 ratios in the on-going and DCM-like groups were significantly higher than those in the control and nonprogressive-disease groups. The CKMM3/CKMM1 ratio was significantly correlated with the annual rate of change for the LV end-systolic dimension (LVDs), LVDd, and LVEF, with the closest correlation observed for the annual change in LVDs. Moreover, 5 patients in the nonprogressive-disease group with elevation of the CKMM3/CKMM1 ratio to $> +2SD$ above the mean for the controls had an elevated annual change in LVDs within $\pm 1SD$ of the mean in the DCM-like group. These results indicate that the ratio of CKMM3 to CKMM1 can be used to predict the progression of LV enlargement in HCM.

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Idiopathic hypertrophic cardiomyopathy (HCM) is characterized by left ventricular (LV) wall hypertrophy, usually with preserved LV wall motion. It is well known that life-threatening arrhythmias and/or sudden death can occur in association with HCM. The incidence and prognostic value of HCM in severe ventricular arrhythmia^{1,2} and sudden death^{3,4} have been extensively studied.

Recently, some researchers^{5,6} including ourselves⁷ have noted that the progression of marked LV enlargement associated with hypofunction resembling

idiopathic dilated cardiomyopathy (DCM) can be found among HCM patients. LV hypofunction due to the progression of LV dilation, as well as life-threatening arrhythmia, is thus very important.

The major histopathological characteristics of typical HCM are myocyte hypertrophy with a disarray of myocyte arrangement⁸ while myocyte necrosis is unusual. In contrast, the myocyte degeneration and/or necrosis followed by fibrotic replacement that is commonly observed in the heart in DCM is observed to some extent in myocardium in HCM associated with

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LV dilation, ie, in DCM-like HCM. These histopathological findings indicate that on-going myocardial damage is present in DCM-like HCM hearts. Detection of this myocardial damage is essential for assessing the risk of the progression of LV enlargement in HCM hearts.

With regard to the detection of myocardial damage, it is well known that creatine kinase (CK) is released from myocytes when myocyte necrosis occurs. Biological studies have revealed that CK is present in the 3 major forms of CKMM, CKMB, and CKBB; CKMM consists of the 3 subunits CKMM 1-3, and the tissue-form subunit is CKMM3. When CKMM is released from the myocardium, the carboxyterminal lysines from 2 subunits are cleaved sequentially by circulatory carboxypeptidase N to convert tissue CKMM3 to circulating CKMM2 and CKMM1^{9,10}. Release of a bolus of myocardial CKMM into the bloodstream increases the relative proportion of CKMM3. Indeed, CKMM3, the CKMM3/total CK ratio and the CKMM3/CKMM1 ratio have all been reported to be highly sensitive for detecting myocardial damage following acute myocardial infarction¹¹⁻¹³.

It can be hypothesized that the continuous release of CK from the myocardium affects the relative proportions of CKMM isoforms. In this study, we measured serum CKMM subunits in patients with HCM with and without LV dilation of various degrees and evaluated the serum levels of CKMM isoforms in an effort to identify a subgroup of patients with HCM that progresses to DCM-like HCM before apparent LV dilation.

Patients and Methods

Patients

The subjects consisted of 35 of a total of 109 patients with HCM admitted to our institution between 1980 and 1988. After excluding patients with poor echocardiographic tracings, age <12 years, or history of myectomy, 51 patients were followed up for more than 3 years (first follow-up period mean $\pm$ SD, 6.5 ± 2.2 years) until 1988 to 1991. Thirty-five of these 51 patients were the subjects of this study. In the other 16 patients, blood samples could not be collected for various practical reasons, such as their failure to visit our hospital again during the period for blood collection or failure to provide informed consent. Serum CKMM isoforms (CKMM1-3), total CK, CKMB, lactate dehydrogenase activity (LDH) and its isoenzyme LDH1 were measured at the end of the first follow-up period in 35 patients who all gave their informed consent, and follow-up (second follow-up

period) was continued until January, 1995. None of these 35 patients presented any neuromuscular disease, significant coronary stenosis demonstrated by coronary angiography, or episodes of angina pectoris. The 35 patients examined consisted of 25 men and 10 women with a mean age of 53 ± 13 years. The control group for serum measurements consisted of 7 men and 4 women, aged 53 ± 6 years. They did not have any heart disease or other disorders which might affect serum measurements, including kidney or liver diseases.

Diagnosis of HCM

M-mode echocardiography and real-time 2-D echocardiography were performed in all of the patients. The diagnosis of HCM was based on the following criteria¹⁴⁻¹⁶: hypertrophied but nondilated left ventricle with characteristic asymmetric hypertrophy; no reduction of the LV ejection fraction (LVEF $\geq 55\%$); and absence of other cardiac or systemic disorders, including hypertension, which could produce secondary LV hypertrophy.

Assessment of Morphologic and Functional Changes

Echocardiographic examination was performed at least annually, and the intraventricular septal thickness (IVST), posterior wall thickness (PWT), LV end-systolic dimension (LVDs), LV end-diastolic dimension (LVDd), and LVEF were measured. Since the annual rates of change of the LV indices during the first and second follow-up periods were not significantly different, the mean annual rate of change of each index was obtained as the slope of the curve for that index by simple linear regression analysis of the annual echocardiographic data acquired from the initial to the final measurement. LVEF was calculated by Teichholz's formula¹⁷.

Definition of Ventricular Size and Hypofunction

We classified the patients into 3 groups: nonprogressive-disease, on-going, and DCM-like groups. Our previous LV morphological and functional follow-up study⁷ demonstrated that an initial decrease in LVDs is followed by both a reduction in LVEF and an enlargement of the LVDd in the progression to the DCM-like heart. According to the results of that study, we classified the patients according to ventricular cavity size and function during the follow-up period as follows: nonprogressive-disease group, LVDd <55 mm and LVEF $\geq 55\%$; on-going group, reduction in LVEF to <55% with LVDd <55 mm; and DCM-like group, reduction in LVEF to <55% with enlargement of LVDd to ≥ 55 mm.

Table 1 Patients Examined, Follow-Up Results and Annual Changes in Echocardiographic Measurements

Total Number of Patients with HCM between 1980 and 1988	109			
Number of Patients followed >3 years	51			
Number of Patients Undergoing Serum Measurements	35			
Group entrance for 35 Patients after 1st Follow-up.	Nonprog. D.G.	On-going G.	DCM-like G.	On-going+ DCM-like Gs
	26	3	6	9
Nonobstructive HCM	23	3	6	9
Obstructive HCM	3	0	0	0
Number of patients dead at the end of 1st Follow-up	0	0	1	1
Annual Changes in Echocardiographic Measurements				
IVS (mm/year)	-0.031±1.042	-0.467±0.378	0.416±0.702	0.122±0.734
PWT (mm/year)	-0.108±0.490	-0.034±0.305	-0.350±0.314	-0.245±0.332
LVDd (mm/year)	0.646±0.977	1.100±0.360*	1.116±0.598*	1.111±0.506*
LVDs (mm/year)	0.354±0.775	1.366±0.550*	1.583±0.741*	1.511±0.656*
LVEF (%/year)	-0.060±1.358	-2.267±0.751*	-1.767±1.191*	-2.022±0.994*
Final Number in Group after 2nd Follow-up	26	2	7	9
Number of Patients who died during 2nd Follow-up	0	0	3	3

Nonprog. D.G., Nonprogressive disease group; On-going G, On-going group; DCM-like G., DCM-like group; IVS, intraventricular septum; PWT, posterior wall thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; * indicates significant difference from the value in nonprogressive disease group.

Measurement of Serum Total CK, LDH, and LDH isoenzyme 1

Total serum CK was measured by a coupled reaction of glucokinase and glucose-6-phosphate dehydrogenase using a diagnostic kit (Iatrotec CK-A; Iatron Laboratories Inc, Tokyo, Japan). CKMB was determined by immunoprecipitation methods using a kit (Iatrotec CK-B; Iatron Laboratories Inc, Tokyo, Japan). An autoanalyzer (Hitachi 7150 Autoanalyzer, Hitachi LTD, Tokyo, Japan) was used to measure serum LDH by enzyme assay with pyruvate and NADH (Kokusaishiyaku, Tokyo, Japan). The isoenzyme of LDH was separated by electrophoresis on cellulose acetate and measured by densitometry.

Measurement of Serum CKMM Isoforms

Serum samples were collected in the morning at rest. CKMM isoforms were assayed in collaboration with SRL Laboratory (Tokyo, Japan) using rapid electrophoresis (Helena Laboratories, Beaumont, Texas, USA) according to the established method^{18,19}. Briefly, a 0.5-μl serum sample was subjected to agarose gel electrophoresis for 15 min with a constant voltage of 1400 V at 10°C. The gel was then incubated for 5 min at 45°C and dried 5 min at 54°C. CKMM subunits were then reacted with PEP CK isoform reagent (Helena Laboratories). The optical densities of CKMM isoforms were finally measured with a densitometer at 417 nm. The intra-assay coefficients of variation for 15 repeated measures of 3 different samples for CKMM1, 2 and 3 were less than

5%, except for one set of measurements (7.8%).

The reproducibility of CKMM isoforms was determined by measuring them twice at approximately 1-month intervals in all of the patients and controls.

Statistical Analysis

The unpaired Student's t-test was used to compare data sets of 2 groups. Simple linear regression analysis was used to assess the correlations between serum measurements and annual changes in LV morphologic and functional parameters. An analysis of variance with Bonferoni's t-test was performed to compare group data. Data are expressed as the mean±SD. A p value of <0.05 was considered statistically significant.

Results

Morphologic and Functional Changes

The clinical courses of the subjects are shown in Table 1.

First follow-up. Among the 35 patients in whom serum CKMM could be measured at the end of the first follow-up period, 26 patients remained in the nonprogressive-disease group, while 3 patients had entered the on-going group and 6 had entered the DCM-like group. One of the 6 patients who had entered the DCM-like group died from congestive heart failure during the first follow-up period. In 5 of these patients, no coronary stenosis was demonstrated by coronary angiography performed at the time of

Table 2 Serum Measurements and Echocardiographic Indices in the 4 Groups at the End of 1st Follow-Up

	control group (n=11)	nonprogressive disease group (n=26)	on-going group (n=3)	DCM-like group (n=6)	on-going+DCM-like groups (n=9)
CK (IU/l)	91.9±25.9	105.4±44.8	112.7±16.7	141.3±48.6	131.8±43.0
CKMB (IU/l)	13.2±5.6	13.3±4.3	16.0±3.6	18.2±3.8	17.4±3.9
LDH (IU/l)	373.4±80.3	338.8±64.9	330.7±39.6	515.3±64.1*	453.8±104.1†
LDH1 (%)	26.4±3.2	25.6±3.3	26.0±1.6	35.2±4.7*	32.1±5.8†
CKMM1 (%)	45.8±7.6	38.6±5.8‡	33.3±3.9‡	33.8±6.1‡	33.7±5.5‡
CKMM2 (%)	23.2±5.1	25.5±3.7	22.3±0.47	25.8±3.5	24.7±3.3
CKMM3 (%)	13.0±3.8	14.9±3.7	19.7±1.7†	19.7±4.4†	19.7±3.7†
CKMM3/CKMM1	0.293±0.095	0.392±0.143‡	0.593±0.069†	0.610±0.204††	0.604±0.171††
Echocardiographic Indices					
IVS (mm)	n.m.	20.5±5.9	17.7±2.4	21.9±7.1	—
PWT (mm)	n.m.	11.4±2.0	10.1±1.1	10.8±2.9	—
LVDd (mm)	n.m.	44.0±3.8	47.8±0.2	62.3±3.1	—
LVDs (mm)	n.m.	26.2±3.9	35.2±1.3	50.8±6.2	—
LVEF (%)	n.m.	68.7±13.9	51.0±4.24	35.8±9.73	—
LAD (mm)	n.m.	41.0±4.6	43.5±4.6	47.9±6.1	—

NS, not significant; IVS, intraventricular septum; PWT, posterior wall thickness; LVDs, left ventricular end-systolic dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; n.m., not measured.

* indicates significant difference from the control, nonprogressive disease and on-going groups ($p<0.05$).

† indicates significant difference from the control and nonprogressive disease groups (†, $p<0.05$; ††, $p<0.01$).

‡ indicates significant difference from the control group ($p<0.05$).

Table 3 Reproducibility of CKMM Isoform Measurements

	CKMM1		CKMM2		CKMM3		CKMM3/CKMM1	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd
mean±SD	39.4±7.4	37.8±7.1	24.7±4.1	25.5±4.3	15.4±4.4	16.0±4.7	0.41±0.17	0.45±0.21
r	0.76		0.62		0.87		0.89	

r, correlation coefficient between at values 1st and 2nd measurements.

entrance into the DCM-like group. Autopsy revealed no stenosis of the coronary artery in the patient who died.

Second follow-up. During the second follow-up period (3.2 ± 0.5 years), the 26 patients in the nonprogressive-disease group at the end of the first follow-up remained in this group. One of the 3 patients in the on-going group entered the DCM-like group. The LV in another patient showed continuous enlargement resembling that in the DCM-like group, and the remaining patient remained in the on-going group. The LVDs showed continuous enlargement similar to that in the on-going group in all 5 patients in the nonprogressive-disease group whose annual change in LVDs was within ± 1 SD from the mean for that in the DCM-like group. During the second follow-up period, 3 patients in the DCM-like group died due to congestive heart failure.

Serum Total CK, CKMB, LDH, and LDH Isoenzyme 1

Table 2 summarizes the serum measurements in the 4 groups at the end of the first follow-up period. There were no significant differences in serum total CK or CKMB. Although patients in the DCM-like group showed elevated LDH and LDH1, there was no significant difference in either LDH or LDH1 between the on-going group and either the nonprogressive-disease group or the control group. Due to the small number of patients in the on-going group and the absence of any significant difference in total CK or CKMB between this group and the DCM-like group, the data for these 2 groups were combined and compared to those in the control and nonprogressive-disease groups. Essentially the same results as were obtained in the comparison of all 4 groups described above were obtained with this combined analysis.

Serum CKMM Isoforms

The results for the reproducibility of CKMM isoform measurements are summarized in Table 3. The correlation coefficient for the CKMM3/CKMM1 ratio at the first and second measurements was 0.89. Clinically acceptable reproducibility was obtained. The mean of the values obtained at the first and second measurements was used for analysis.

The relationships between CKMM isoforms and other cardiac-associated measurements, such as total CK, CKMB, LDH and LDH1, are summarized in Table 4. CKMM1 and CKMM2 were weakly corre-

Table 4 Correlation Coefficients: CKMM1, CKMM2 and CKMM3 to Total CK, CKMB, LDH and LDH1

	Total CK	CKMB	LDH	LDH1
CKMM1	0.35*	0.30*	NS	NS
CKMM2	0.37*	0.34*	NS	NS
CKMM3	NS	NS	NS	NS
CKMM3/CKMM1	NS	NS	NS	NS

* indicates significant correlation ($p < 0.05$). NS, not significant.

lated with total CK and CKMB.

Although CKMM1 and the CKMM3/CKMM1 ratio were significantly elevated in the nonprogressive-disease group compared to those in the control group, a substantial overlap of values was noted. The CKMM3/CKMM1 ratios in the on-going and DCM-like groups were significantly higher than those in the control and nonprogressive-disease groups (Fig 1A). The smallest overlap of the range for any serum measurement was observed for the CKMM3/CKMM1 ratio in the on-going or DCM-like group with that in the nonprogressive-disease group. The CKMM3/CKMM1 ratio in the DCM-like group was not different from that in the on-going group. In 5 patients in whom the serum CKMM3/CKMM1 ratio was elevated more than 2SD above the mean in the control group, the annual change in LVDs (indicated as closed triangles in Fig 1) was 1.28 ± 0.40 mm/year; this annual change was within ± 1 SD from the mean for that in the DCM-like group. One patient in the DCM-like group showed a CKMM3/CKMM1 ratio within ± 2 SD from the mean for that in the control group. This patient showed a relatively low annual rate of change

Fig 1. The CKMM3/CKMM1 ratio in each of the 4 groups (A) and the relationship between this ratio and annual changes in LVDs (B), Cont, control group; Nonprog, nonprogressive-disease group; On-going, on-going group; DCM-like, DCM-like group. Closed triangles indicate patients in the nonprogressive-disease group whose CKMM3/CKMM1 ratio was more than +2SD above the mean for the control group (dotted line). Open triangles indicate patients in the nonprogressive-disease group whose CKMM3/CKMM1 ratio was below this cutoff.

Table 5 Probability Values and Correlation Coefficients Obtained in Simple Correlation Analysis for Serum Measurements and Annual Changes in Echocardiographic Indices

	<i>Annual Change</i>					
	<i>LVDs</i>		<i>LVDd</i>		<i>LVEF</i>	
	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>
CK	NS		NS		NS	
CKMB	NS		NS		NS	
CKMM1	0.0072	-0.447	NS		0.0074	0.455
CKMM2	NS		NS		NS	
CKMM3	0.0047	0.467	NS		0.0331	-0.361
CKMM3/CKMM1	0.0001	0.622	0.0107	0.426	0.0022	-0.501
LDH	NS		NS		NS	
LDH1	NS		NS		NS	

p, probability value; *r*, correlation coefficient; NS, not significant; LVDs, left ventricular end-systolic dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction.

for LVDs compared to the other 5 patients in the DCM-like group. Conversely, in patients in the nonprogressive-disease group whose annual change in LVDs was less than 1 SD below the mean for the DCM like-group, the CKMM3/CKMM1 ratio (0.351 ± 0.129) was not different from that for the controls. Only one of these patients showed an LVDs which was more than 2SD above the mean for the controls. When the data for the on-going group and DMC-like group were combined, essentially the same results were obtained.

Relationship Between Serum Measurements and Echocardiographic Indices

Table 5 summarizes the results of the correlation between serum measurements and the annual changes in echocardiographic indices obtained using data for all of the subjects. Linear regression analysis revealed that the CKMM3/CKMM1 ratio was correlated with annual changes in LVDs, LVDd and LVEF. The highest correlation was observed for the relationship between the CKMM3/CKMM1 ratio and the annual change in LVDs (Fig 1B).

Discussion

The main findings of this study were a significant elevation of the CKMM3/CKMM1 ratio in the on-going and DCM-like groups, a correlation between this ratio and annual changes in LVDd, LVEF, and particularly LVDs, and a high annual rate of change in LVDs in 5 patients with a high CKMM3/CKMM1 ratio in the nonprogressive-disease group. These findings indicate that the serum CKMM isoform is a predictive indicator of the progression of LV enlargement with a reduction in LVEF (progression to DCM-like heart) in

patients with HCM.

We classified our HCM patients into 3 groups based on the results of our previous study⁷, which had demonstrated that HCM patients include a subgroup with LV enlargement and reduced LV wall motion. The results of another study also support this concept of the initial enlargement of LVDs²⁰. In this group, the LVDs enlarges initially; thus, only patients with a reduction in LVEF were included in the on-going group.

Seven patients entered the DCM-like group at the end of the second follow-up, and the incidence of the progression of LV enlargement seemed to be high. The study was conducted in 35 of the original total of 109 patients, and it is possible that the other 74 patients were asymptomatic and without LV morphological changes, since they did not continue to seek treatment at our hospital. If these 74 patients are included in the nonprogressive-disease group, the incidence of LV enlargement is 6.4% in our patients with HCM, which is comparable to values given in previous reports^{6,20}.

In our study, the CKMM3/CKMM1 ratio was significantly higher in the on-going and DCM-like groups than in the nonprogressive-disease group. Only 2 previous studies have measured serum CKMM isoforms in patients with HCM, and these studies did not include any comparison of serum CKMM isoforms between patients with HCM and DCM-like HCM. Therefore, the present results cannot be directly compared with the findings of these earlier studies.

The CKMM3/CKMM1 ratio in patients with HCM was significantly higher than that in the control patients. This result was also reported by Hamada et al²¹ and Teragaki et al²². Despite this significant difference, the values showed considerable overlap. This raises the question of whether the nonprogressive-disease

group examined in this study or those in other HCM studies included HCM patients who were in transition to on-going or DCM-like status. Five patients in the nonprogressive-disease group with an elevated CKMM3/CKMM1 ratio also showed elevated annual changes in LVDs. Conversely, patients in the nonprogressive-disease group whose annual change in LVDs was depressed compared to that in the DCM-like group showed a CKMM3/CKMM1 ratio comparable to the control value. Therefore, the inclusion of patients with HCM undergoing transition to on-going or DCM-like status could account for the results in previous reports that the CKMM3/CKMM1 ratio in patients with HCM is higher than that in controls, but with considerable overlap. This indicates that our nonprogressive-disease group probably included patients entering on-going or DCM-like status.

A pathological study⁸ has demonstrated that myocyte degeneration and necrosis with fibrotic changes are observed in DCM-like HCM hearts. However, these changes are not observed in HCM hearts with normal LV size and function. Thus, continuous myocardial damage may occur in the DCM-like HCM heart. This would account for the high CKMM3/CKMM1 ratio in the on-going and DCM-like groups.

The CKMM3/CKMM1 ratio was significantly correlated with LVDs, LVDd and LVEF, as well as with annual changes in these indices. We could find no reports of a similar analysis, and therefore could not compare the present results with those in previous studies. Our results indicate that CKMM reflects myocardial damage and is accordingly correlated with parameters which reflect morphological changes. Among echocardiographic indices, an increase LVDs is initially observed during the progression to DCM-like heart.^{7,20} Therefore, a change in LVDs is an important predictor for the progression of LV enlargement. Among serum measurements, the CKMM3/CKMM1 ratio showed a relatively strong correlation with the annual change in LVDs. The correlation of this ratio with the morphological index that is most highly correlated with the progression to DCM-like heart indicates that this ratio fairly well reflects myocardial damage in HCM hearts.

We are unable to account for the higher sensitivity of the CKMM3/CKMM1 ratio to the progression of LV enlargement in HCM compared to other cardiac enzymes, such as total CK, CKMB and LDH1, although weak correlations were observed between both CKMM1 and CKMM2 and total CK and CKMB. Studies on acute myocardial infarction have demonstrated that this ratio is among the first serum

measurements, including CK, total CK, and LDH, to increase. These results suggest that the CKMM3/CKMM1 ratio reflects myocardial damage during the early period when damage would be moderate. The same high sensitivity has also been reported in skeletal muscle.²³ This might be due to the stability of the conversion and disappearance of CKMM isoforms.

One of the limitations of this study was that because the incidence of the progression of LV enlargement in HCM is relatively low, we examined a relatively small number of patients. However, the results seem reasonable not only statistically but also in terms of consistency at repeated follow-up. No other cardiac-specific enzyme, such as myosin light chain or troponin T, was measured in this study and their sensitivities for the detection of LV enlargement in HCM cannot be compared with that of the CKMM3/CKMM1 ratio.

In summary, the CKMM3/CKMM1 ratio is a predictive indicator of the progression of LV enlargement in patients with HCM.

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