

VENTRICULAR FUNCTION

Systolic Outward Motion of the Left Ventricular Apical Wall as Detected by Magnetic Resonance Tagging in Patients with Apical Hypertrophic Cardiomyopathy

Masaki Tsukamoto, MD,¹ Satoshi Hirasaki, MD,¹ Toshiro Kuribayashi, MD,² Akiko Matsuo, MD,² Hiroyuki Matsui, MD,²
Takahisa Sawada, MD,² Takashi Nakamura, MD,² Akihiro Azuma, MD,² Hiroki Sugihara, MD,²
and Hiroaki Matsubara, MD²

¹Department of Cardiology, Akashi Municipal Hospital, Hyogo, Japan,

²Department of Cardiology and Vascular Regenerative Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

ABSTRACT

Patients with apical hypertrophic cardiomyopathy (APH) associated with paradoxical jet flow (ie, diastolic flow away from the apex) may gradually develop an apical aneurysm, which often leads to arrhythmia and mural thrombus formation. We observed systolic outward motion of the left ventricular apical myocardium in patients with APH using a magnetic resonance tagging procedure and examined the relationship of the outward motion to echocardiographic and scintigraphic findings and to cardiac events. Systolic displacement of the myocardial tags of the apical region perpendicular to the long axis in the 4-chamber view was recorded in 31 patients with APH. Of these patients, 14 showed no outward movement of tags (group A), and 17 showed outward movement (group B). In group B, apical hypertrophy was more severe (35 ± 7 mm vs. 29 ± 6 mm, $p < 0.05$), paradoxical jet flow was more frequent (64% vs. 14%, $p < 0.05$) and the defect score in I-123-beta-methyliodophenylpentadecanoic acid scintigraphy was higher (2.1 ± 0.7 vs. 1.3 ± 0.7 , $p < 0.01$). During a mean follow-up period of 55 months, only 1 patient experienced paroxysmal atrial fibrillation in group A. In group B, 1 patient died suddenly, 1 was admitted to hospital because of congestive heart failure, 2 developed angina pectoris, 2 exhibited non-sustained ventricular tachycardia, and 1 showed multifocal premature ventricular contraction; in these 7 patients the outward movement was greater than in the 10 patients in Group B who had no cardiac events (1.00 ± 0.59 vs. 0.52 ± 0.40 , $p < 0.05$). Hence, our results show that outward tag displacement is frequently associated with severe apical hypertrophy, paradoxical jet flow, apical ischemia, and cardiac events. The tagging method may be useful in assessing the severity of APH and predicting the occurrence of cardiac events at an early stage.

INTRODUCTION

Apical hypertrophic cardiomyopathy (APH) is characterized by cardiac hypertrophy localized to the left ventricular (LV) apical region and a spade-like configuration in the right oblique projection of the left ventriculogram (1). The clinical course of most patients with APH is not unfavorable (2, 3), but some patients develop an apical aneurysm over a long period of time, accompanied by cardiac events such as arrhythmia, mural thrombus formation and systemic embolism (4–9). Our echocardiographic studies (7, 10) suggested that LV cavity obstruction by a hypertrophied myocardium causes sequestration of the apical chamber

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Correspondence to:

Masaki Tsukamoto, M.D.

Department of Cardiology

Akashi Municipal Hospital

1-33, Takasho-cho, Akashi-shi, Hyogo

Japan

email: mtsukam@nifty.com

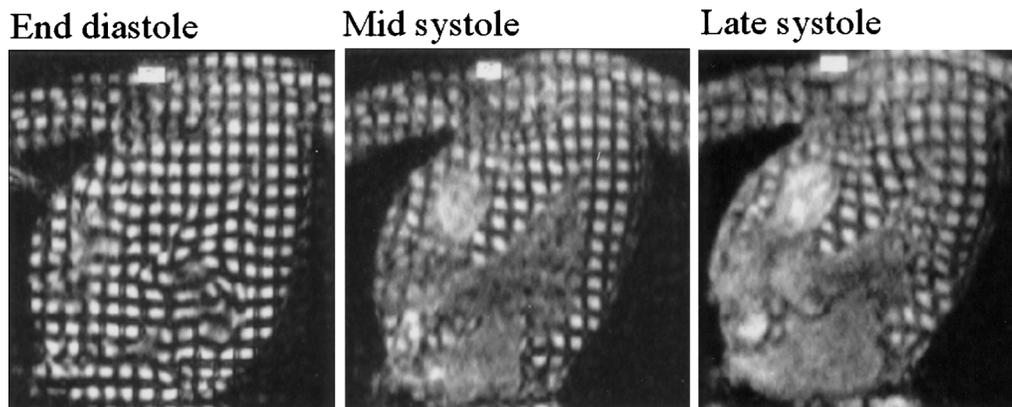


Figure 1. Myocardial tagging. Images collected in three phases were used for analysis. End diastole was determined by synchronizing with the peak of the R wave on the electrocardiogram. Mid-systole and late systole were defined as 100 msec and 200 msec after end diastole, respectively.

followed by paradoxical jet flow and that concurrent high mural pressure then leads to myocardial injury and apical aneurysm, resulting in adverse clinical events.

Echocardiography and left ventriculography can be used to detect paradoxical jet flow and a discrete apical chamber, respectively (7, 10). On the other hand, magnetic resonance (MR) imaging can be used to visualize the details of myocardial morphology and deformation throughout the heart. Myocardial MR tagging has been used to evaluate segmental wall motion in ischemic heart disease and hypertrophic cardiomyopathy (11–13), and we have previously applied this method to APH and observed systolic outward movement of myocardial tags in the apical region (14). In the current paper, the clinical significance of the outward movement is assessed in APH patients using echocardiography, scintigraphy and correlation with cardiac events.

METHODS

Patients

The patients comprised 25 males and 6 females with APH (mean age, 58 years old; range, 30–78 years old). The patients underwent the MR study from April 1994 to November 1999. Diagnosis of APH was based on echocardiography findings of hypertrophy located mainly in the LV apical region and on the spade-like configuration of the LV. No patient exhibited either significant coronary stenosis in coronary angiography or any other cardiovascular disease. Two patients had a family history of hypertrophic cardiomyopathy. Informed consent was obtained from all patients, and the study protocol was approved by the Research Committee of our institution.

Myocardial tagging

The MR study was performed using a 1.5-Tesla system (Magnetom H15 Siemens, Munich, Germany) with the patient in the supine position. The tags were labeled at the end diastole, synchronized with the peak of the R wave on the electrocardio-

gram. Tagging images were obtained in the four-chamber view from the end diastole to the end systole with spatial modulation of magnetization under the following conditions: repetition time, 50 msec; echo time, 9 msec; flip angle, 50°; matrix size, 128 × 256 pixels; average, 3; field of view, 300; slice thickness, 7 mm; and tag size, 7 mm. Neither synchronization with respiratory motion nor holding of breath was used during the recording of tagging images; this reflects the relatively dated nature of the equipment used, compared to that currently available.

The long axis of the LV was defined as the line joining the apex to the center of the mitral ring. The LV was then divided into 3 equal segments along the axis: the apical, middle and basal segments. Images at end diastole, mid-systole, and late systole were used for analysis, with mid- and late systole being defined as 100 msec and 200 msec after end diastole, respectively (Fig. 1). The movement of each tag of the apical segment was traced on a monitor and the average displacement of tags perpendicular to the long axis was calculated during early systole (from end diastole to mid-systole) and late systole (from mid-systole to late systole) (Fig. 2). To normalize the magnitude of tag displacement, the phase-to-phase displacement of the center of gravity was subtracted from each tag displacement, using the mean of the coordinates of all LV tags as the center of gravity in each phase.

Measurement of apical wall thickness

Cine MR images produced by a gradient-echo sequence were also obtained in the four-chamber view. Apical wall thickness was determined as the sum of the septum and lateral wall thickness of the apical region in the end diastolic image.

Echocardiography

Prior to the MR analysis, an echocardiographic study was performed to detect paradoxical jet flow (10), using a Toshiba SSH 160A (Toshiba Corp., Tokyo, Japan) or Hewlett-Packard Sonos 1500 and 5500 (Hewlett-Packard, Bothell, WA). Paradoxical jet flow is recognized as a high flow signal at the site of obliteration

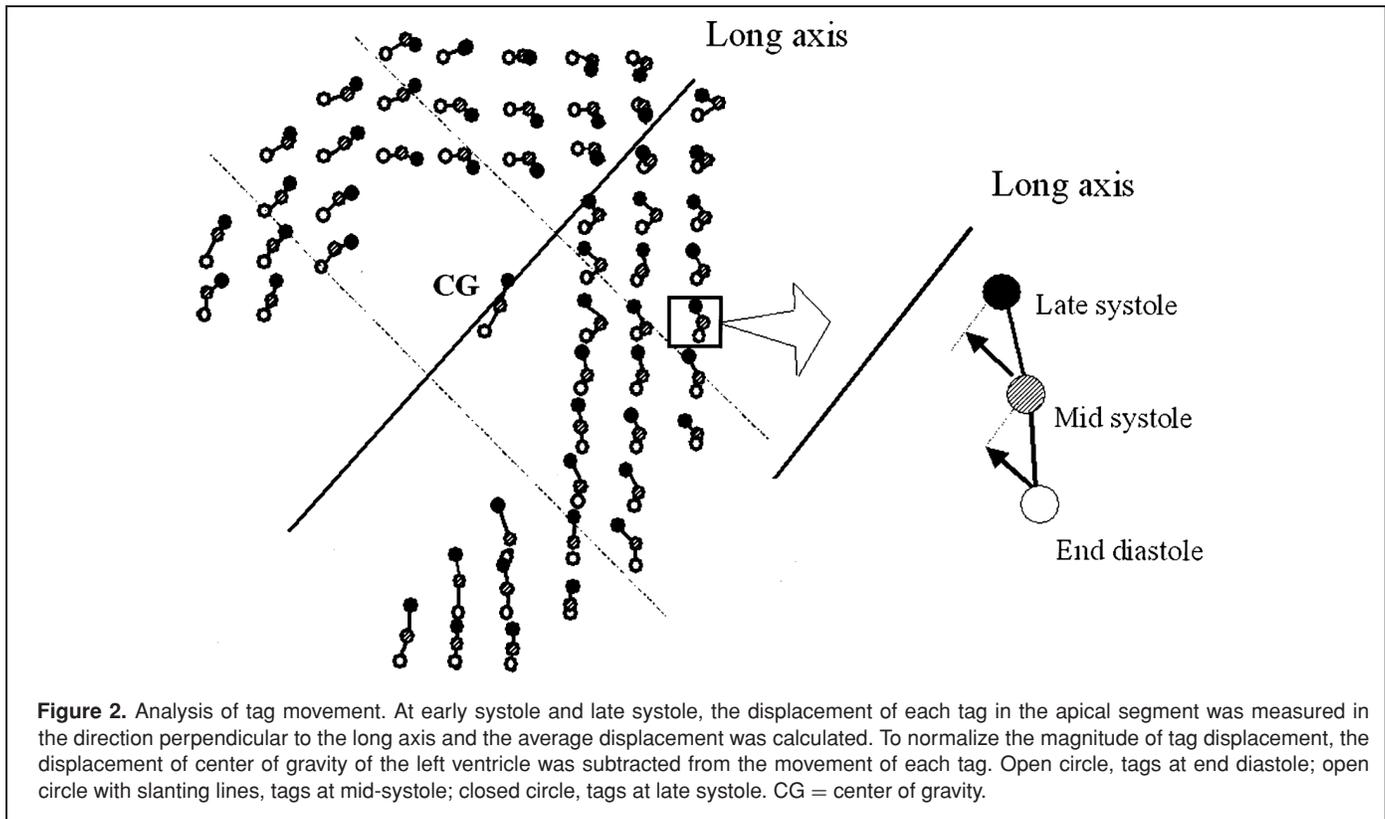


Figure 2. Analysis of tag movement. At early systole and late systole, the displacement of each tag in the apical segment was measured in the direction perpendicular to the long axis and the average displacement was calculated. To normalize the magnitude of tag displacement, the displacement of center of gravity of the left ventricle was subtracted from the movement of each tag. Open circle, tags at end diastole; open circle with slanting lines, tags at mid-systole; closed circle, tags at late systole. CG = center of gravity.

of the LV cavity, directed away from the apex toward the base during diastole. We searched for this phenomenon using a 2.5-MHz transducer (Toshiba Corp., Tokyo, Japan or Hewlett-Packard, Bothell, WA) in the four-chamber view, with the patient in the left decubitus position.

Myocardial scintigraphy

I-123-beta-methylidophenylpentadecanoic acid (BMIPP) and exercise stress thallium-201 (Tl) scintigraphy were performed using a bicycle ergometer within 1 month of the MR study.

Single photon emission tomography (SPECT) images were obtained 30 minutes after injection of 111 MBq of BMIPP in the fasting state. Apical uptake of BMIPP on the vertical long axis of the image was visually graded by three experienced observers based on a defect score: 0, normal; 1, mildly reduced; 2, severely reduced; 3, no uptake. Interobserver disagreements were resolved by consensus.

Exercise stress began at 25 W and increased by 25 W every 3 minutes with the end point being the target heart rate, physical exhaustion, or development of chest pain. One minute before termination of exercise, 111 MBq of Tl was injected intravenously. SPECT images were obtained 15 minutes and 4 hours after termination of exercise. Apical uptake of thallium was assessed in the same way as that described for BMIPP scintigraphy.

Cardiac events

Cardiac events were investigated in 19 patients from the time of the MR analysis until June 2005. Twelve patients were not

followed to the end of the study period, since they discontinued visiting our hospital. The mean follow-up period was 55 months (range, 2–109 months), and the patients' clinical records at the hospitals they attended were used to obtain the relevant information. Arrhythmia was also investigated using a 24-hour ambulatory electrocardiogram, which was applied simultaneously with the MR analysis and then repeated at least every 12 months thereafter.

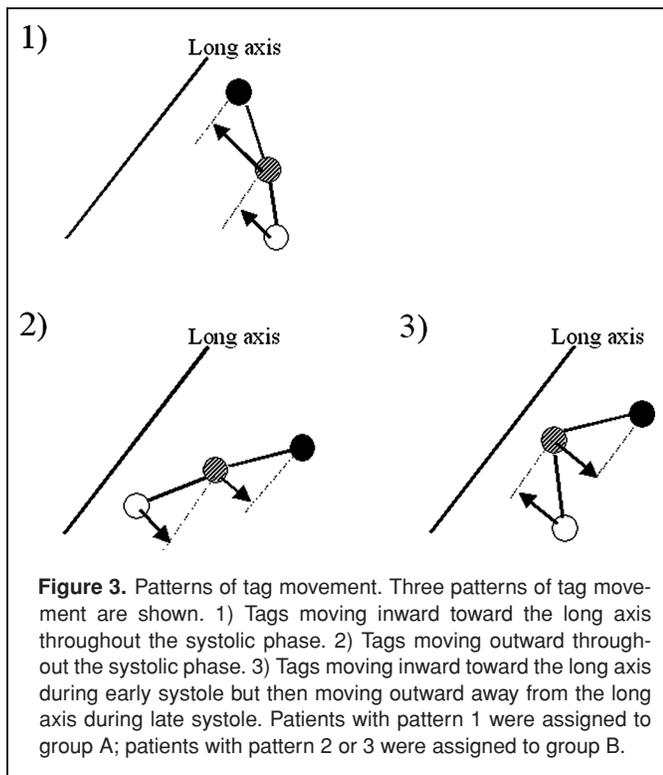
Statistical analysis

Continuous variables are expressed as means \pm standard deviation and compared by unpaired *t* test. Correlations of tag displacement with wall thickness and scintigraphic defect score were determined by linear regression analysis and Kendall rank correlation, respectively. Differences in the BMIPP and Tl defect scores between groups A and B were assessed by Mann-Whitney U test. The prevalence of paradoxical jet flow in the two groups was compared by Fisher's exact test. A *p* value <0.05 was considered statistically significant.

RESULTS

Displacement of tags

Analysis of tag displacement revealed 3 patterns (Fig. 3), as follows: pattern 1, in which tags moved inward toward the LV long axis throughout the systolic phase (14 patients); pattern 2, in which tags moved outward away from the long axis throughout the systolic phase (4 patients); and pattern 3, in which tags moved



inward toward the long axis during early systole but then moved outward away from the long axis during late systole (13 patients).

Patient classification

The 14 patients showing tag movement of pattern 1 (no outward movement) were assigned to group A, and the remaining 17 patients with tag movement of patterns 2 or 3 (with outward movement) were assigned to group B.

Apical wall thickness, paradoxical jet flow, and myocardial scintigraphy in relation to outward displacement (Figs. 4 and 5)

Apical wall thickness was significantly greater in group B than in group A (35 ± 7 mm vs. 29 ± 6 mm, respectively, $p < 0.05$). There was a significant correlation between the outward displacement of tags and apical wall thickness during late systole ($r = 0.41$, $p < 0.05$). Paradoxical jet flow was observed in 11 (64%) of the 17 patients in group B, but in only 2 (14%) of the 14 patients in group A ($p < 0.05$). BMIPP scintigraphy was recorded in all 14 patients in group A and in 14 of the 17 patients in group B. The BMIPP defect score in the apical segment was significantly higher in group B than in group A (2.1 ± 0.7 vs. 1.3 ± 0.7 , $p < 0.01$), and was significantly correlated with the outward displacement of tags during late systole ($\tau = 0.28$, $p < 0.05$). Nine of the 14 patients in group A and 11 of the 17 patients in group B also underwent Tl scintigraphy under exercise stress. There was neither a significant difference in the defect score between groups A and B nor a significant correlation between the defect score and the outward displacement of tags during late systole in either the exercise or redistribution images.

Cardiac events (Table 1)

The mean follow-up period was 47 months in group A and 62 months in group B. Cardiac events were seen in 1 (7%) of the 14 patients in group A and in 7 (41%) of the 17 patients in group B. The patient in group A had a history of asymptomatic paroxysmal atrial fibrillation. Of the 7 patients with cardiac events in group B, 1 died suddenly (probably due to a cardiac event), 1 was admitted to hospital due to congestive heart failure, 2 developed angina pectoris, 2 exhibited non-sustained ventricular tachycardia (6 or more consecutive ventricular premature beats, lasting for less than 30 seconds), and 1 exhibited multifocal premature ventricular contraction.

Tag movement in relation to cardiac events and paradoxical jet flow (Fig. 6)

The outward displacement of apical tags during late systole in group B was significantly greater in the 7 patients with cardiac events than in the 10 patients without such events (1.00 ± 0.59 mm vs. 0.52 ± 0.40 mm, $p < 0.05$). All 4 patients who exhibited outward tag displacement throughout the systolic phase (pattern 2) experienced cardiac events, including sudden death. There was no significant difference in the magnitude of outward displacement between the 11 patients with paradoxical jet flow and the 6 patients without paradoxical jet flow (0.76 ± 0.56 mm vs. 0.63 ± 0.54 mm, $p = 0.65$). Of the 7 patients with cardiac events, 6 exhibited paradoxical jet flow.

CASE PRESENTATION

A typical example of systolic outward movement observed in a 69-year-old man is shown in Fig. 7. In this case, the apical wall was very thick (36 mm), BMIPP scintigraphy demonstrated severely reduced uptake in the apical segment, and paradoxical jet flow was observed by echocardiography.

DISCUSSION

Systolic outward movement of tags is considered to reflect systolic outward wall motion. This peculiar wall motion is easily understood in the 11 patients of group B who displayed paradoxical jet flow, which is thought to be due to systolic sequestration of an apical chamber at high pressure and diastolic release of its contents. It has been suggested that an apical chamber, but not necessarily an aneurysm, is sequestered because of systolic cavity obstruction and muscular squeezing at the mid-ventricular to apical regions. Such behavior should occur in the presence of asynchronized LV contraction, ie, delayed contraction on the apex side of the obstruction (7, 10). The pressure in the apical chamber is increased by squeezing and may exceed the systolic contractile force of the apical myocardium, causing it to move outward during systole.

Paradoxical jet flow was not observed in 6 of 17 patients exhibiting outward tag movement in group B. An apical chamber with no resultant paradoxical jet flow will not be produced when

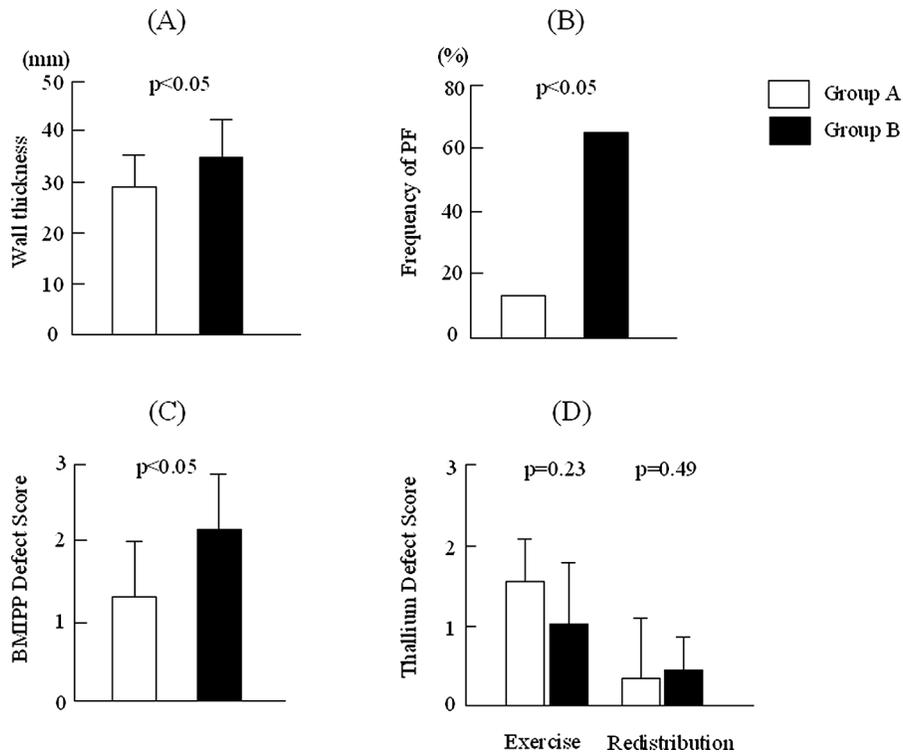


Figure 4. Apical wall thickness, paradoxical jet flow and scintigraphic defect score in groups A and B. (A) Apical wall thickness was more severe, (B) paradoxical jet flow was more frequent, and (C) BMIPP defect score was higher in group B, compared to group A. There was no significant difference in (D) thallium defect score between the 2 groups. BMIPP = I-123-beta-methylidophenylpentadecanoic acid; PF = paradoxical jet flow.

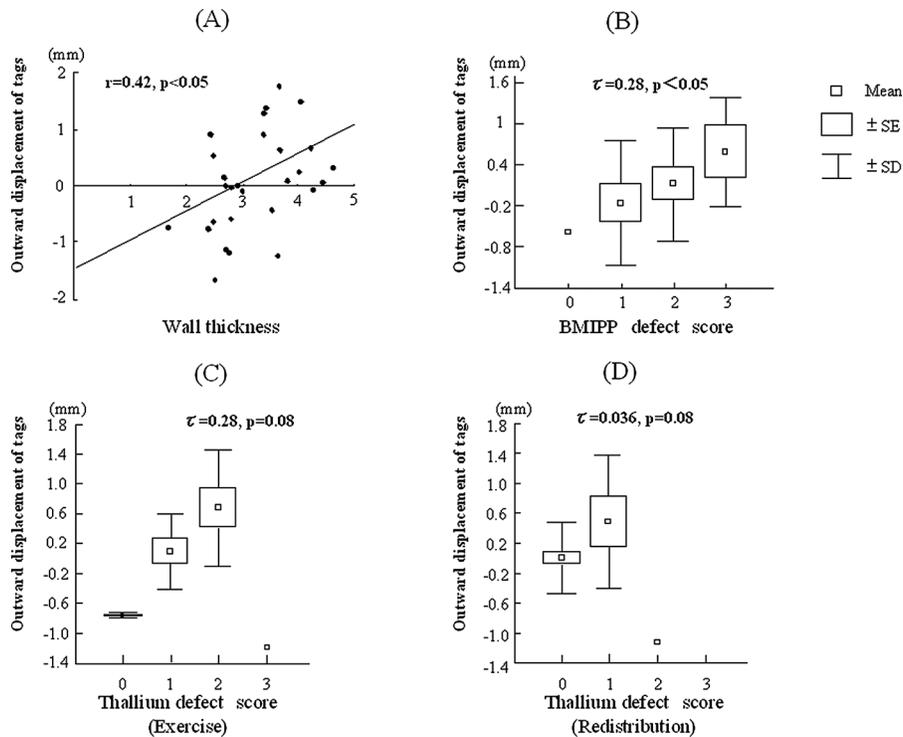


Figure 5. Correlation of tag movements with other parameters. Outward displacement of tags was significantly correlated with (A) apical wall thickness and (B) BMIPP scintigraphic defect score, but not with (C and D) thallium scintigraphic defect score.

Table 1. Patients experiencing cardiac events

Case	Event	BMIPP defect score	Paradoxical Jet flow	Group
1. 49 y.o. male	Sudden death	not examined	(+)	B
2. 62 y.o. male	Non-sustained ventricular tachycardia	2	(+)	B
3. 57 y.o. male	Non-sustained ventricular tachycardia	3	(+)	B
4. 60 y.o. male	Congestive Heart Failure	2	(+)	B
5. 63 y.o. female	Anginal pain	2	(+)	B
6. 64 y.o. male	Anginal pain	2	(-)	B
7. 55 y.o. male	Multifocal premature ventricular contraction	not examined	(+)	B
8. 69 y.o. male	Paroxysmal atrial fibrillation	2	(-)	A

Group A, patients with no outward movement of apical tags.

Group B, patients with outward movement of apical tags.

BMIPP = I-123-beta-methylidophenyl pentadecanoic acid.

the LV wall contracts in the normal manner and apical obliteration occurs simultaneously with or earlier than the obstruction and squeezing on the basal side of the apical region. In this scenario, the apical myocardium will also move outward if squeezing on the basal side of the apical portion is stronger than the contractile force of the apical myocardium. In this context, it is of note that the magnitude of outward tag movement in patients without paradoxical jet flow did not differ significantly from that in patients with paradoxical jet flow.

A marked BMIPP defect of the apical segment in group B suggests the presence of myocardial ischemia. It has been reported that apical hypertrophy and cavity obliteration cause latent myocardial injury through high mural pressure and

ischemia (6, 8–10). Here, this applies to those hearts with systolic outward motion since cavity obstruction and squeezing on the basal side of the apical region will lead to a high mural pressure in this region, regardless of the presence or absence of a sequestered chamber (15, 16). High mural pressure will impede coronary flow not only during systole but also during diastole due to the persistence of high apical mural pressure for some time after early diastole when the cavity obstruction and squeezing is resolved. Furthermore, resolution of the cavity obstruction and squeezing will be delayed due to impaired relaxation as a consequence of a hypertrophied myocardium.

It has also been reported in patients with hypertrophic cardiomyopathy (17, 18) that severely reduced uptake or accumulation of BMIPP is associated with myocardial injury and cardiac events. Myocardial ischemia also plays an important role in the natural history of hypertrophic cardiomyopathy (19–21) due to its characteristics of low capillary density, cellular hypertrophy, and myocardial disarray (22): factors which will additionally promote myocardial ischemia in patients with APH. There was no significant difference in impairment of thallium uptake, which was much less severe than that of BMIPP, as already demonstrated and discussed in our previous study on hypertrophic cardiomyopathy (23).

Our results suggests the presence of a vicious circle, in which cavity obliteration, myocardial squeezing and mural pressure elevation are exacerbated through myocardial hypertrophy and ischemia, until myocardial damage, fibrosis and wall thinning ultimately release the heart from the circle. Thus, as APH advances, myocardial ischemia and damage may develop into aneurysm formation. At this stage, apical outward motion during systole is a reflection of apical dyskinesia or paradoxical wall motion because of the inability of the aneurysm to contract actively. This argument may be compatible with our observation that cardiac events occurred mostly in patients exhibiting outward movement of MR tags, with the magnitude of the outward movement being greater in patients with cardiac events than in those without such events.

Clinical significance of outward movement of MR tags

We have already demonstrated that cardiac and adverse clinical events including systemic embolism occur more frequently in patients with APH and also in those with paradoxical jet flow (10). Paradoxical jet flow and apical chamber sequestration can often be detected by echocardiography and left ventriculography, but segmental outward motion of the myocardium or pressure elevation in the obliterated cavity is much more difficult to detect. Furthermore, an apical chamber and paradoxical jet flow are not necessarily produced or detected even in the presence of squeezing and high mural pressure, as stated above. Thus, demonstration of apical outward motion by means of MR tagging may be more useful than echocardiography or left ventriculography for early prediction of development of myocardial damage, aneurysm formation, and cardiac events.

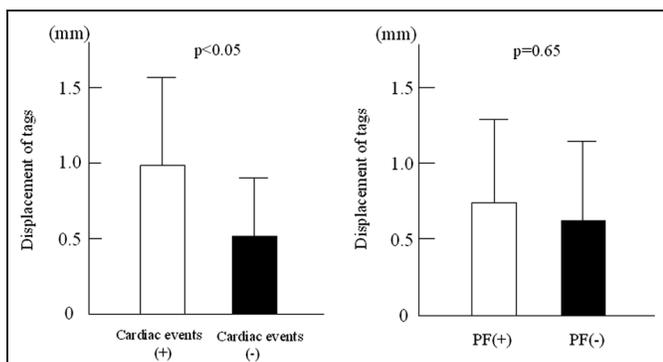


Figure 6. Tag movement in relation to cardiac events and paradoxical jet flow. Of 17 patients with outward tag movement, the 7 patients with cardiac events had greater outward tag displacement during late systole, compared to the 10 patients without cardiac events (left). There was no significant difference in outward displacement between 11 patients with paradoxical jet flow and 6 patients without paradoxical jet flow (right). PF = paradoxical jet flow.

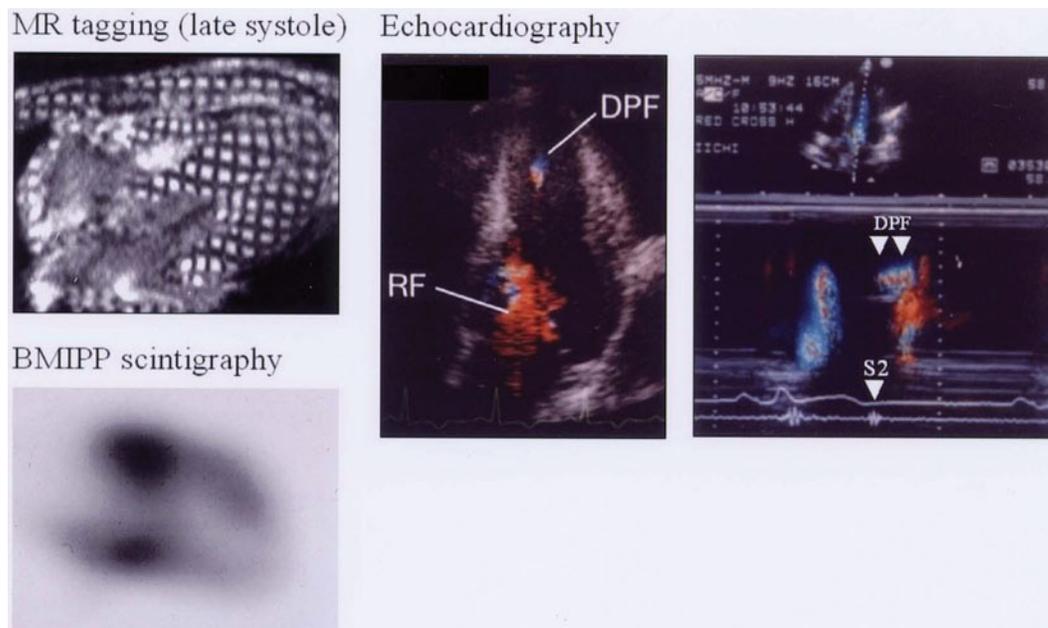


Figure 7. Typical case of APH with systolic outward movement of MR tags. The MR image displays severe apical hypertrophy. In this patient, the apical wall thickness was 36 mm, apical uptake of BMIPP was severely reduced, and echocardiography showed paradoxical jet flow at early diastole, directed away from the apex toward the base. DPF = diastolic paradoxical jet flow; RF = rapid filling; S2 = second heart sound.

Study limitations

The magnitude of tag movements was normalized by subtracting the movement of the center of gravity of the LV from each tag movement. In most studies of myocardial tagging, the center of gravity moves toward the apex and the ventricular septum, as shown in Fig. 2. Thus, unless the tag movement is normalized by the method presented here, outward movement of the tags in the lateral wall tends to be canceled out and outward movement in the ventricular septum tends to be overestimated. The current study represents the first quantification of outward movement of myocardial tags, and therefore the method of normalization remains to be verified through further multiple studies.

CONCLUSION

Outward displacement of tags was frequently associated with severe apical hypertrophy, paradoxical jet flow, apical ischemia, and cardiac events. The tagging method may be useful in assessing the severity of APH and predicting the occurrence of cardiac events at an early stage.

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