Detection of Viable Myocardium by Dobutamine Stress Tagging Magnetic Resonance Imaging With Three-Dimensional Analysis by Automatic Trace Method

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The present study attempted to detect the viability of myocardium by quantitative automatic 3-dimensional analysis of improvement of regional wall motion using an magnetic resonance imaging (MRI) tagging method. Twenty-two subjects with ischemic heart disease who had abnormal wall motion on echocardiography at rest were enrolled. All patients underwent dobutamine stress echocardiography (DSE), coronary arteriography and left ventriculography. The results were compared with those of 7 normal volunteers. MRI studies were done with myocardial tagging using the spatial modulation of magnetization technique. Automatic tracing with an original program was performed, and wall motion was compared before and during dobutamine infusion. The evaluation of myocardial viability with MRI and echocardiography had similar results in 19 (86.4%) of the 22 patients; 20 were studied by positron emission tomography or thallium-201 single photon emission computed tomography for myocardial viability, or studied for improvement of wall motion following coronary intervention. The sensitivity of dobutamine stress MRI (DSMRI) with tagging was 75.9% whereas that of DSE was 65.5%. The specificity of DSMRI was 85.7% (6/7) and that of DSE was 100% (7/7). The accuracy of DSMRI was 77.8% (28/36) and that of DSE 72.2% (26/36). DSMRI was shown to be superior to DSE in terms of evaluation of myocardial viability. (Jpn Circ J 2000; 64: 487–494)

Key Words: Dobutamine stress MRI; Tagging; 3-D analysis

The aim of the present study was to evaluate the validity of magnetic resonance imaging (MRI) with tagging during dobutamine infusion for determining myocardial viability and to compare this method with dobutamine stress echocardiography.

Patients with severe coronary artery disease, either after acute myocardial infarction or not, have abnormal asynergic left ventricle wall motion. Sometimes it is difficult to make a clear decision regarding intervention, such as percutaneous transluminal coronary angioplasty (PTCA), or surgery, such as coronary artery bypass grafting (CABG), because the myocardial viability cannot be assessed easily. Various conditions of the myocardium, such as recovery, infarct necrosis, myocardial stunning (abnormal wall motion, normal flow) and myocardial hibernation (abnormal wall motion, persistent ischemic flow) can occur. Chronic resting ventricular dysfunction may be indicative of either necrotic or viable myocardium. Recently, there have been many reports on the detection of viability (stunned myocardium or hibernating myocardium) by echocardiography with inotropic stimulation or nuclear techniques such as thallium-201 (201TI) single photon emission computed tomography (SPECT) or positron emission tomography (PET). With regard to dobutamine stress tests, there have been several reports on low-dose dobutamine stress testing for detection of viable myocardium, primarily performed by echocardiograph; however obesity or emphysematous changes in some patients can affect the diagnostic utility of this method. In addition, a quantitative evaluation is not possible from echocardiography. As for nuclear medicine, it is expensive and there are unsolved problems about nuclear intervention.

By contrast, MRI can reveal clear images of the ventricular wall, including the lateral portion, in almost all patients. However, there have been few quantitative analyses of wall motion using MRI with inotropic stimulation because it is a time-consuming procedure and considerably more time is required to analyze MRI when using spatial modulation of magnetization (SPAMM), even though the SPAMM tagging methods are very useful for a precise analysis of wall motion. Therefore, in the present analysis, we used an original program created with the programming language 'Visual Basic', which traced all intersecting points of the tags easily and automatically. We then analyzed left ventricular wall motion using low-dose dobutamine stress MRI in normal volunteers as well as in patients with ischemic heart disease. We then attempted to detect the viability of the myocardium by a quantitative analysis of the improvement of the regional wall motion using a visible and comprehensive 3-dimensional (3-D) method.

Methods

Study Population

Twenty-two patients, 19 males and 3 females, with ischemic heart disease, were enrolled in the present study. Their average age was 69.2 years, and all of them had abnormal ventricular wall motion on echocardiography at rest. Nine patients with acute myocardial infarction (AMI)
were included. All of them were also studied by dobutamine stress echocardiography (DSE), coronary arteriography, and left ventriculography, and they also underwent low-dose dobutamine stress MRI on the same or next day. Patients with AMI were studied 4 weeks after its onset. As controls, 7 normal male volunteers with an average age of 29.1 years were also studied. These volunteers had normal ECGs and no history of abnormal cardiac events. The nature and purpose of the study and risks involved were explained to the patients and volunteers, and informed consent was obtained from all subjects before the study.

Cardiac Catheterization
Coronary angiography and biplane cine-ventriculography were performed according to the Judkins technique, and multiple views of each artery were obtained. Two or 3 independent observers who were unaware of the clinical data analyzed the angiograms, expressing coronary artery narrowing as percent diameter stenosis, with significant coronary artery stenosis defined as >75% lumen narrowing. Nine patients had 1-vessel disease, 6 had 2-vessel disease and 6 had 3-vessel disease. One patient had no significant coronary artery stenosis. All patients demonstrated wall motion abnormalities at rest during biplane ventriculography.

Dobutamine Stress Echocardiography
Patients were studied by DSE either on the same day or the day before dobutamine stress MRI. Dobutamine was infused with a volumetric pump at doses of 5, 10, 20, 30, 40μg·kg⁻¹·min⁻¹ at incremental steps of 3 min. A 12-lead ECG and arterial blood pressure were recorded at basal conditions and at the end of each stage. Two-dimensional (2-D) echocardiographs (in standard multiple short-axis, long-axis, and 4-chamber long-axis views) were recorded on videotape at rest and during dobutamine infusion. We stopped the infusion of dobutamine at the point of the appearance of chest pain, any other symptoms, ischemic change on the ECG, abnormal increase or decrease of blood pressure or heart rate, or the appearance of asynergic wall motion. The images were digitized and stored on an optical disk for display in a quad-screen format. A 16-segment model of the left ventricle, constructed according to the recommendations of the American Society of Echocardiography, was used to evaluate left ventricular wall motion and wall thickness during systole. Each segment was graded on a scale of 1–4 (1, normal or hyperkinesis; 2, hypokinesis; 3, akinesis; 4, dyskinesis). Two observers, who were blinded to the patients' clinical data, evaluated the echocardiograms. A third observer was asked in cases of disagreement, and a majority decision was reached. The test results were considered positive for the presence of viable myocardium if ≥1 dysynergic segment had ≥1 increase of wall motion score compared with the resting echocardiogram during dobutamine infusion at the doses of 5 or 10μg·kg⁻¹·min⁻¹.

Dobutamine Stress MRI With Tagging
To avoid any trouble, patients underwent DSE up to 40μg·kg⁻¹·min⁻¹ on either the same day or the day before dobutamine stress MRI. The patients showing symptoms or an abnormal ECG or any other trouble during DSE up to 20μg·kg⁻¹·min⁻¹ did not undergo dobutamine stress MRI. The MRI studies were done using the Signa Advantage or Horizon with a 1.5 Tesla magnet by GE with ECG triggering. The images were acquired in a double oblique orientation (short-axis, long-axis, 4 chamber long-axis planes). The short-axis view is acquired at half of the distance from the base to the apex. Three sections including long-axis, short-axis, and 4 chamber long-axis views were obtained with myocardial tagging using the SPAMM technique before and during dobutamine infusion. A cine-MRI with SPAMM tagging sequence (echo time 17 ms; slice thickness 10 mm; FOV 35x35 cm; matrix 256x152; 2 NEX; the interval of tagging 7 mm) was used with a pixel size of 1.4x2.3 mm, (the pixel size was calculated FOV and matrix), and the number of phases per heart cycle were 16. The time interval of each phase was 26 ms, and the first phase was acquired at 13 ms after the R wave. The stress imaging was done in exactly the same orientation and level by saving the acquisition parameters of the 3 resting views (Fig 1). The patients were not allowed to move between the examinations. Dobutamine was infused at a dose of 5μg·kg⁻¹·min⁻¹. Stress MRI was started after 3 min of dobutamine infusion and the heart rate and rhythm were monitored throughout. Dobutamine stress 2-D echocardi-
programs were obtained either on the same day or on the previous day.

**Analysis of MRI With Tagging**

Five images of 3 planes from the MRI studies each were used for analysis. From 16 images of cine-MRI tagging, an image at 65 ms after the R wave of ECG was taken first, and then 4 consecutive images at 52 ms intervals were obtained. The last image was at 273 ms, reaching the limitation of precise analysis of tagging. We used the first image as the diastolic phase, and the last image as the systolic phase.

We used an original program created by Isao Saito using the programming language 'Visual Basic' on a DOS/V machine. First we manually traced the endocardium and epicardium of the left ventricle in the diastolic and systolic phases to examine wall thickening and manually traced all intersecting points of tags on the myocardium in all the sequential 5 images. Next we again traced all intersecting points of the tags on the myocardium, using this original auto-tracing program, which showed no significant difference from manual tracing.

The wall motion was compared before and during dobutamine infusion in the 20 patients and 7 normal subjects using the following 3 methods of analysis. First, we obtained the wall-thickening ratio, which was derived from dividing the systolic left ventricular wall thickness by the diastolic thickness from the 3 sections including long-axis, short-axis and 4 chamber long-axis views. In each of the 3 sections, we divided the left ventricle into 5 areas and then automatically measured the thickness of the left ventricle at the 4 other evenly divided segments in each area, and the results were averaged and used as the thickness of each area. Second, we obtained the distance of wall motion in all 5 areas of each of the 3 sections, each area included approximately 5–8 intersecting points of tagging. Third, we obtained the shortening rate calculated by the circumferential distance between tags during systole multiplied by that during diastole averaged on all tags in all 5 areas of each of the 3 sections. In the control studies, we were able to achieve a precise evaluation and so could evaluate the myocardial viability by comparing the distance of movement of tags in control and patients both before and during dobutamine infusion.

**3-D Reconstruction**

The data from the tag motion in the 3 sections are available in 3-D reconstruction (Fig 2). After the 3-D reconstruction, tags are analyzed according to 3-D motion, and the distance of intersection of tags is determined from 3-D tracings.

**Definition of Viability in Dobutamine Stress MRI**

We divided 5 areas into 3 sections each (short-axis, long-axis, 4 chamber long-axis planes). Initially, the 3-D reconstructed distance of the traced intersections of tags was analyzed in the control subjects. Then each area was divided into 5 scores of motion by half SD (standard deviation in the control studies).

*Tag-movement Score*

Score 1 (in each segment, the distance of movement of tags of patients by the distance of normal subjects was <AV (Average in control studies)−5/2×SD); Score 2 (similarly, tag-movement was AV−5/2×SD−AV−3/2×SD); Score 3 (tag-movement was AV−3/2×SD−AV−1/2×SD); Score 4 (tag-movement was AV−1/2×SD−AV+1/2×SD); Score 5 (tag-movement was >AV+1/2×SD). In the dobutamine stress MRI, we defined a viable segment according to the following rules: rule 1: a score of 1, 2 or 3 before dobutamine; and rule 2: an improvement in any of the scores by 1 point or more during dobutamine. If this improvement was seen, recovery of motion during dobutamine infusion in the asynery area was ascertained.

**Viability and Follow-up**

To determine viability, 19 of the 22 patients underwent 201TI SPECT, 14 patients were examined by PET, and follow-up echocardiography without the use of dobutamine was performed in 10 patients 1 month after CABG or PTCA. Twenty patients were tested more than once. We estimated viability, from rest redistribution thallium scintigraphy performed 4h later, by the existence of metabolism of the myocardium on the fluorodeoxyglucose-PET, and by the improvement of wall motion after CABG or PTCA. Some patients were evaluated for viability by 2 or even all 3 examinations, and the estimation by these methods showed no discrepancies in any of the patients.

**Statistical Analysis**

A probability value of less than 0.05 was considered to be statistically significant. Statistical analysis of the changes of the wall-thickening ratio, the distance of motion of tags, and the shortening rate between the control state and dobutamine perfusion in the normal volunteers was performed using the Student’s paired t test.

**Results**

**Normal Subjects (Table 1)**

In the normal control subjects, the wall-thickening ratio at the baseline of the left ventricle was higher than at the apex in the vertical long-axis view, and at the free wall was higher than at the septum in the short-axis view. In the horizontal long-axis view, it was slightly higher at the free wall than at the septum and apex. The thickening ratio in the
Table 1  Results of 3 Analyses of Normal Subjects

<table>
<thead>
<tr>
<th>Distance of normals (mm)</th>
<th>Wall thickness ratio</th>
<th>Circumferential shortening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before dobutamine</td>
<td>During dobutamine</td>
</tr>
<tr>
<td></td>
<td>5.34*</td>
<td>5.56**</td>
</tr>
<tr>
<td>Long axis view</td>
<td>3.63*</td>
<td>3.70**</td>
</tr>
<tr>
<td>Segment 1</td>
<td>2.640</td>
<td>3.32*</td>
</tr>
<tr>
<td>Segment 2</td>
<td>5.602</td>
<td>6.292*</td>
</tr>
<tr>
<td>Segment 3</td>
<td>8.026*</td>
<td>8.735*</td>
</tr>
<tr>
<td>Short axis view</td>
<td>3.564*</td>
<td>3.71**</td>
</tr>
<tr>
<td>Segment 1</td>
<td>3.637</td>
<td>3.797</td>
</tr>
<tr>
<td>Segment 2</td>
<td>3.205</td>
<td>3.964</td>
</tr>
<tr>
<td>Segment 3</td>
<td>4.199</td>
<td>4.848</td>
</tr>
<tr>
<td>Segment 4</td>
<td>4.225*</td>
<td>4.735*</td>
</tr>
<tr>
<td>Segment 5</td>
<td>7.091*</td>
<td>7.315*</td>
</tr>
<tr>
<td>4-chamber view</td>
<td>4.653</td>
<td>4.76</td>
</tr>
<tr>
<td>Segment 1</td>
<td>2.888</td>
<td>3.409</td>
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<tr>
<td>Segment 2</td>
<td>5.239</td>
<td>5.615</td>
</tr>
<tr>
<td>Segment 3</td>
<td>8.272*</td>
<td>8.84</td>
</tr>
</tbody>
</table>

In each of the 3 sections, we divided the left ventricle into 5 segments, each used for analysis. In the normal control subjects, the wall-thickening ratio increased significantly with dobutamine infusion in all 15 segments. Similarly, the distance of movement of intersecting points of tags showed a significant increase in normal subjects. In addition, in most areas, the circumference shortened, and all areas shortened more during dobutamine infusion. (*p<0.05).

Fig 3. The thickening ratio in normal subjects increased significantly with dobutamine infusion (p<0.05). The left light bars are the thickening ratio before dobutamine, and the right dark bars are during dobutamine. During dobutamine infusion in all segments, the distance of movement of tags showed a significant increase in normal subjects. The wall thickening at the base of the left ventricle is greater than at apex in the vertical long-axis view, and at the free wall is greater than at the septum and apex.

normal subjects increased significantly with dobutamine (Fig 3). Similarly, the distance of movement of the intersecting points of tags at the base of the left ventricle was greater than at the apex in the vertical long-axis view, and at the free wall was greater than at the septum and apex. But in the short-axis view, the distance of movement of tags was not different in any of the 5 areas. Furthermore, during dobutamine infusion in all segments, the distance of movement of tags showed a significant increase in normal subjects (Fig 4), and in most areas, the circumference shortened and all areas shortened even more during dobutamine infusion (Fig 5).

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Fig 4. The left light bars are the distance of movement before dobutamine, and the right dark bars are during dobutamine. The distance of movement (mm) of intersecting points of tags at the basement of the left ventricle is greater than at apex in the vertical long-axis view, and at the free wall is greater than at the septum and apex. However, in the short-axis view, the distance of movement of tags did not differ in the 5 areas. Furthermore, during dobutamine infusion in all segments, the distance of movement of tags showed a significant increase in normal subjects.

Fig 5. The left light bars are the circumference shortening before dobutamine, and the right dark bars are during dobutamine. In all areas, the circumference shortened, and shortened even more during dobutamine infusion in most areas. But in the short-axis view, there is no significant shortening during dobutamine infusion.
Inferior MI Viability(-)

Before Dobutamine

During Dobutamine

Fig 6. Inferior wall infarction without viability. In this case, the wall motion was hypokinetic both before and during dobutamine.

Anterior MI Viability(+)

Before Dobutamine

During Dobutamine

Fig 7. In this case, the wall motion was hypokinetic before dobutamine, but became normal during dobutamine. After PTCA, the motion in the anterior wall changed to normal by echocardiograph.

Ischemic Cases

There was no trouble during dobutamine stress MRI. A case of inferior wall infarction without viability is shown in Fig 6 in which the wall motion was hypokinetic both before and during dobutamine, and so we decided that there was no viability in the inferior wall in this case. Another case was viable in the anterior wall (Fig 7), and in that case, the motion was hypokinetic before dobutamine, but normalized during dobutamine. In fact, we studied the wall motion of this case with echocardiography at 1 month after PTCA, and the motion in the anterior wall had improved. The results of the evaluation of myocardial viability with dobutamine stress MRI and echocardiography were similar in 19 (86.4%) of the 22 patients with ischemic heart disease. Among these 22 patients, 20 were studied by PET, 201TI SPECT, or were examined for improvement in wall motion.
following coronary intervention. To estimate the viability with the correspondence between DSE and MRI, in each patient we designated 3 vessel areas.  

1. The LAD area involves areas no. 1–3 in the long-axis section, no. 1 and 2 in the short-axis section and no. 1–3 in the 4-chamber section.  
2. The LCX area involves area of no. 3 in the short-axis section, and areas no. 4 and 5 in the 4-chamber section.  
3. The RCA area involves areas no. 4 and 5 in the long-axis section, and areas no. 4 and 5 in the short-axis section.  

Therefore, we estimated the viability in 60 vessel-areas in the 20 patients (Figs 3–5). In the 20 patients with myocardial viability, we estimated that there were 36 asynergic vessel-areas in the 60 vessel-areas. The sensitivity of dobutamine stress MRI with tagging was 75.9% (22/29) and that of DSE was 65.5% (19/29). The specificity of dobutamine stress MRI was 85.7% (67/77) whereas that of DSE was 100% (7/7). The accuracy of MRI was 77.8% (28/36) and DSE 72.2% (26/36).

Discussion

There are some reports on the assessment of the improvement of wall motion by inotropic stimulation with MRI compared with echocardiography or nuclear techniques but there are few quantitative analyses concerning wall motion assessment from cine-MRI with inotropic stimulation because it is a time-consuming method with even more time required to analyze the MRI using SPAMM, which provides a precise regional analysis of wall motion.

We overcame this problem of time by developing an original program for the analysis of SPAMM tagging. This program can trace all the tags on the left ventricle wall automatically and then reconstructs the motion of the left ventricle in 3-D from the long-axis, vertical long-axis, and short-axis views, easily providing data about cardiac function in ischemic heart disease.

Noninvasive SPAMM tagging permits precise and direct visualization of wall motion and of shortening within the left ventricular wall. Furthermore, transmural wall motion can also be evaluated. Some clinical cases present with abnormal wall motion and stenosis of coronary arteries, so it is occasionally necessary to decide between intervention PTCA or CABG on the basis of whether the myocardium is viable. Invasive treatment should be avoided if possible, from the point of view of risk as well as cost. However, it is difficult to differentiate viable myocardium, such as stunned or hibernating myocardium, from necrosis infarction. At present, low-dose dobutamine echocardiography or other nuclear intervention techniques are used, but these methods may be high cost, have lower precision and the conditions such as obesity or pulmonary emphysema can affect the value of the data obtained. In the present study there were 2 obese patients and in 1 case the viability of the inferior wall was misdiagnosed only on echocardiography. However, there were no significant data of the viability between echocardiography and MRI in each of the 3 vessel areas.

From our control studies we obtained minute data of transmural wall motion, and then, by using it as the standard, we could precisely detect the viable myocardium, equal to or superior to low-dose DSE. We used the distance of the movement of tags to detect the viability in a comparison with controls and there are a number of approaches for detecting the viability in tagging MRI. For example, some use the deformity of the square from 4 tags to study the cardiac function, and others use the deformity of the triangle from 3 tags. In the present study, first with the normal controls, 3 methods were used to analyze the cardiac function in wall motion; that is, the distance of the movement of tags, the wall thickening rate, and the circumferential shortening rate. From these 3 methods, cardiac function was seen to be significantly hyperkinetic during dobutamine infusion compared with before dobutamine. With the ischemic patients, we used the method of the distance of tag movement because it is relatively simple to perform, and the result was superior to DSE.

In the present study, the sensitivity of DSE tended to be low and the specificity to be high compared with other studies, which is inexplicable, but may be due to the sensitivity and specificity changing in proportion to the number of patients studied.

In routine clinical work, it is necessary to use simple and quick procedures to reach a diagnosis and this method is the best for distinguishing between viable and nonviable myocardium. In ischemia, a nonviable area may move similarly to an adjacent viable area, but by comparison with normal controls, they can be distinguished; the viable area moves more than the nonviable area because accumulated motion is observed.

Further studies are required to improve the sensitivity. There are 3 problems. The first is the analysis of the tagging, in which the sensitivity may be increased by using the deformity of the triangle from 3 tags or the square from 4 tags. The next problem is the total estimation from the distance of the movement of the tags, wall thickness, the circumferential shortening. And the final problem is the dose of dobutamine. To avoid any trouble, we infused dobutamine up to a rate of 5 μg·kg⁻¹·min⁻¹, but if we infused dobutamine until 10 μg·kg⁻¹·min⁻¹ was reached, as in echocardiography, the sensitivity may increase. In the present study, the viability did not match in 7 vessel-areas on MRI, which may have been caused either by the precision of MRI (a pixel size of 1.4×2.3 mm) or the methods of analysis, and will also be solved in further studies.

Study Limitations

One limitation is that it required a long acquisition time during dobutamine stress MRI, taking 4–5 min per slice per patient, and the total examination time was 40–50 min per patient. This problem may be solved by high-speed MRI techniques. Another drawback is the time of the appearance of tagging on the left ventricle wall. The tags remain on the wall for up to 350 ms, but as the automatically available and precise image data from the tags in all patients was only up to 270 ms, they could not be observed until the
end of the systole. This problem also will be resolved by improvement of the pulse sequences in the future. Finally, we have 3 standards for viability: improvement of wall motion after intervention, SPECT and PET. Ideally, they should all be applied to each patient, but because of the various conditions of the patients and their rehabilitation schedules, this was not practical. In our subsequent study, we intend to designate the improvement of wall motion as the golden standard.

Conclusions

In summary, DSE, which is often used for evaluating myocardial viability, sometimes fails to demonstrate clear images because of obesity or pulmonary emphysema. In contrast, quantitative evaluation of left ventricular wall motion in every segment was possible with low-dose dobutamine stress MRI by the tagging method. Therefore, the MRI procedure is superior to echocardiography for evaluating myocardial viability.

References


Japanese Circulation Journal Vol.64, July 2000