Stress/Rest Circumferential Strain in Non-Ischemia, Ischemia, and Infarction
– Quantification by 3 Tesla Tagged Magnetic Resonance Imaging –

Tomoyuki Kido, MD; Michinobu Nagao, MD; Teruhito Kido, MD, PhD; Akira Kurata, MD, PhD; Masao Miyagawa, MD, PhD; Akiyoshi Ogimoto, MD, PhD; Teruhito Mochizuki, MD, PhD

Background: Adenosine triphosphate (ATP) induces relative hypoperfusion in significantly stenotic coronary arteries, but its effect on myocardial strain has not been used clinically for the detection of ischemia. The purpose of this study was to quantify ATP-stress-induced contractile impairment as altered myocardial strain in coronary artery disease (CAD) using tagged magnetic resonance (MR) and to evaluate its diagnostic capability in comparison with ATP-stress myocardial perfusion-MR.

Methods and Results: Tagged MR and perfusion-MR under ATP-stress and rest conditions and late gadolinium enhancement (LGE) MR imaging were performed in 22 patients with suspected CAD. The peak absolute value of the circumferential strain (C-strain) was measured in 12 segments. Myocardial segments were categorized as non-ischemic (n=201), ischemic (n=42), or infarcted (n=21) according to the perfusion-MR and LGE MR imaging results. The absolute C-strain was significantly greater under ATP-stress (19±13%) (mean±SD) than under at-rest (15±11%, P<0.001) conditions in non-ischemic segments. Conversely, the absolute C-strain was significantly lower under ATP-stress (10±13%) than under at-rest (16±6%, P<0.01) conditions in ischemic segments. Optimal cutoff values for stress C-strain (~17.5%) could successfully differentiate segments with ischemia or infarction from non-ischemic ones with a sensitivity of 86%, a specificity of 65%, and an area under the curve of 0.79.

Conclusions: C-strain analysis using tagged MR could detect ATP-stress-induced contractile impairment in ischemic myocardium. (Circ J 2013; 77: 1235–1241)

Key Words: Magnetic resonance imaging; Myocardial infarction; Myocardial ischemia; Myocardial perfusion imaging; Ventricular function

Cardiovascular magnetic resonance (CMR) is a valuable imaging modality that can be used to investigate ventricular function, myocardial perfusion, viability, and coronary artery anatomy during a single examination, without radiation exposure. Stress myocardial perfusion-magnetic resonance (MR), using a gadolinium-based contrast agent, is a sensitive method for detecting coronary artery disease (CAD) with good specificity. Recently, several studies have tested the accuracy of stress perfusion-MR for the detection of CAD and have shown equal or improved results compared with single-photon emission computed tomography (SPECT). Late gadolinium enhancement (LGE) MR imaging (MRI), with its high spatial resolution and high contrast-to-noise ratio, can also detect myocardial infarcts with high diagnostic accuracy. However, the presence and extent of LGE is associated with an increased risk of cardiovascular events in patients with CAD. A combination of LGE and myocardial perfusion-MR can provide structural and physiological information that helps in the diagnosis of CAD and has been applied clinically. On the other hand, cine MRI provides accurate and reproducible measurements of cardiac function and is currently regarded as the reference standard. Currently, tagged MR offers a reproducible measure of regional myocardial strain that can be used for a detailed analysis of regional ventricular function with high spatial resolution and accuracy.

Adenosine triphosphate (ATP) induces hyperemia in normal coronary arteries and relative hypoperfusion in stenotic coronary arteries. Its effect on myocardial wall motion has been studied, but the effect on myocardial strain has not been elucidated quantitatively by tagged MR.
4 women; mean age, 28±3 years) were enrolled as a control group. For the controls, tagged MR under ATP-stress and at-rest conditions was performed using the same imaging parameters as for the patient group.

**CMR Imaging Protocol**

All studies were performed using a clinical, whole-body, 3 Tesla MR scanner (Achieva 3.0 T Quasar Dual; Philips Healthcare, Best, the Netherlands) equipped with a dedicated cardiac software package and a 32-element cardiac phased-array coil (16 posterior elements, 16 anterior elements), and a 4-lead vector cardiomap was used for cardiac gating. The CMR imaging protocol used in this study is shown in Figure 1. After acquisition of scout images, at-rest tagged images were obtained in 3 short-axis images of the left ventricle (basal, mid, and apical) using a 2D turbo field-echo sequence with a rest-grid pulse. Imaging parameters were as follows: repetition time, 4.7 ms; echo time, 2.8 ms; flip angle, 12°; section thickness, 8 mm; field of view, 380 mm; matrix size, 288×195; sensitivity encoding (SENSE) factor, 2.5; tag grid, 6.0 mm; and 20 cardiac phases/R-R interval on ECG. After 3 min of ATP infusion (0.14 mg·min⁻¹·kg⁻¹ body weight), a gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist; Schering, Germany) was administered intravenously at 0.05 mmol/kg body weight (injection rate, 4 ml/s), followed by a 30-ml saline flush, administered at the same rate. ATP-stress perfusion-MR was performed during every cardiac cycle over the first pass; images were acquired over 35 s. A perfusion sequence was acquired in 3 identical, short-axis locations using a 2D T1 turbo field-echo sequence with the k-space and time broad-use line acquisition speed-up technique (k-t BLAST). Imaging parameters were as follows: repetition time, 3.7 ms; echo time, 1.85 ms; flip angle 20°; section thickness, 8 mm; field of view, 400 mm; matrix size, 256×179; and k-t BLAST factor, 5. ATP-stress tagged MR was then performed continuously using an imaging sequence identical to that used for the at-rest tagged MR. After 10 min, the same perfusion imaging sequence, with a second dose of gadopentetate dimeglumine (0.05 mmol/kg body weight [total dose 0.1 mmol/kg]) was repeated without ATP-stress to obtain at-rest perfusion images. LGE images were obtained in locations identical to those used for tagged imaging by using an inversion-recovery 3D T1 turbo field-echo sequence 10 min after the second contrast administration. The imaging parameters for this part of the study were as follows: repetition time, 3.5 ms; echo time, 1.69 ms; inversion time,

| Table 1. Characteristics of the Patients With Coronary Artery Disease |
|---------------------------------|------------------|
| Characteristic                  | Value            |
| No. of patients                 | 22               |
| Age (years; mean ± SD)          | 61.3±14.1        |
| Male sex                        | 12 (55%)         |
| Hypertension                    | 12 (55%)         |
| Hyperlipidemia                  | 8 (36%)          |
| Diabetes mellitus               | 5 (23%)          |
| Family history                  | 4 (18%)          |
| Smoking                         | 9 (41%)          |
| BMI                             | 23.5±4.0         |
| LVEF (%)                        | 55.8±11.4        |
| LVEDV (ml)                      | 125.4±43.6       |
| LVESV (ml)                      | 59.0±38.6        |

Data are n (%) unless otherwise shown.

BMI, body mass index; LVEF, left ventricular ejection fraction; LVEDV, Left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

clinically for the detection of ischemia. The purpose of the present study was to quantify the contractile impairment induced by ATP-stress using tagged MR and to evaluate the diagnostic utility of this method for detecting CAD in comparison with ATP-stress myocardial perfusion-MR and LGE MRI.

**Methods**

**Study Population**

The study protocol was reviewed and approved by the institutional review board of the university, and written informed consent was given by all patients and volunteers involved in this study. Between March 2011 and November 2011, a total of 35 consecutive patients with suspected CAD underwent CMR using ATP-stress and were registered in the study. The patients had to refrain from coffee, tea, chocolate, and other caffeinated beverages for at least 24 h before undergoing CMR examination; 13 patients with a history of coronary artery bypass grafting (CABG) and cardiomyopathy were excluded from further participation in the study. As a result, 22 patients (12 men, 10 women; mean age, 61±14 years) were prospectively enrolled (Table 1). In addition, 11 healthy volunteers (7 men,
was defined as an area with a perfusion defect (>25% of wall thickness) under ATP-stress, normal perfusion at rest, and non-LGE in delayed images (Figure 3). An infarcted segment was defined as an area with a perfusion defect under ATP-stress and the presence of LGE (>25% of wall thickness). A non-ischemic segment was defined as an area with normal perfusion under ATP-stress and at-rest, and non-LGE in delayed images. If the same segment was deemed both ischemic and infarcted, the determination was based on views on either side. Control segments corresponded to those in normal volunteers; the 11 volunteers did not show any non-ischemic segments.

Statistical Analysis
Continuous data are expressed as means ± SD. The differences in the C-strain values between ATP-stress and at-rest conditions in each group were analyzed using the Wilcoxon signed-rank test. The differences in the C-strain values between any 2 of the 4 groups were analyzed using the Steel-Dwass test. The diagnostic capability of the C-strain for CAD was ana-

**Figure 2.** Tagged images and time-curves of circumferential-strain (C-strain) under adenosine triphosphate (ATP)-stress and at-rest conditions in a 28-year-old healthy female volunteer. Short-axis, mid-ventricular view of tagging at-rest (A) and under stress (B) at end-systole. The x-axis indicates the time frames (20 frames/cycle) and the y-axis indicates the C-strain values (C, D). Tagged images show an increase in wall motion and the absolute peak C-strain value becomes elevated under ATP-stress conditions.
ues in ischemic segments were significantly lower under ATP-stress (10±13%) than at-rest (16±6%, P<0.01) conditions. The absolute C-strain mean value in infarcted segments was lower under ATP-stress (4±12%) than at-rest (9±7%) conditions, but the difference was not significant (P=0.17) (Figure 4).

Comparison of C-Strain Values Among Non-Ischemic, Ischemic, Infarcted, and Control Segments
Under both ATP-stress and at-rest conditions, the absolute C-strain values in the infarcted segments were significantly lower than those in the control, non-ischemic, and ischemic segments. Under ATP-stress, the absolute C-strain values in the non-ischemic segments were significantly greater than those in the ischemic segments. However, under at-rest conditions, there was no difference between the ischemic and non-ischemic segments (Table 2). Additionally, the absolute C-strain values in the control segments were significantly greater than those in non-ischemic, ischemic, and infarcted segments under both ATP-stress and at-rest conditions.

The differences in C-strain values between ATP-stress and at-rest conditions (∆C-strain) in non-ischemic and control segments (4±15% and −5±10%, respectively) were significantly smaller than the ∆C-strain values in segments with ischemia.
ATP is a naturally occurring vasodilator that has been used to induce maximal coronary hyperemia. It also induces an elevated heart rate and may lead to hyperkinesis. Coronary hyperemia induced by ATP infusion has been reported to result in hyperkinetic wall motion in normal myocardium. The increase in C-strain under ATP-stress conditions compared with determinations made under at-rest conditions. ATP is a naturally occurring vasodilator that has been used to induce maximal coronary hyperemia. It also induces an elevated heart rate and may lead to hyperkinesis. Coronary hyperemia induced by ATP infusion has been reported to result in hyperkinetic wall motion in normal myocardium. The increase in C-strain under ATP-stress conditions compared with determinations made under at-rest conditions.

Table 2. Absolute Peak C-Strain Values During ATP-Stress and At-Rest CMR Imaging Conditions Among Ischemic, Non-Ischemic, and Infarcted Segments

<table>
<thead>
<tr>
<th>Segment</th>
<th>No. of segments</th>
<th>Rest C-strain (%)</th>
<th>P value</th>
<th>Stress C-strain (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ischemic</td>
<td>201</td>
<td>14.6±10.8</td>
<td></td>
<td>18.6±13.0</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>42</td>
<td>16.4±6.2</td>
<td>NS</td>
<td>9.7±13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarcted</td>
<td>21</td>
<td>8.6±6.7</td>
<td>&lt;0.01</td>
<td>3.9±11.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P value: difference with respect to non-ischemic segments. ATP, adenosine triphosphate; CMR, cardiovascular magnetic resonance; C-strain, circumferential strain.

Discussion

To our knowledge, this is the first clinical study to quantitatively analyze contractile impairment in coronary arteries induced by ATP-stress in segments with ischemia or infarction using ATP-stress tagged MR. By using this approach, we found that, in the non-ischemic or control segments, the absolute C-strain values increased significantly under ATP-stress conditions compared with determinations made under at-rest conditions. ATP is a naturally occurring vasodilator that has been used to induce maximal coronary hyperemia. It also induces an elevated heart rate and may lead to hyperkinesis. Coronary hyperemia induced by ATP infusion has been reported to result in hyperkinetic wall motion in normal myocardium. The increase in C-strain under ATP-stress in non-ischemic and control segments, as indicated in Figure 4, correlates with the physiological status under ATP-stress conditions.

Figure 4. Absolute circumferential-strain (C-strain) differences between stressed and at-rest tagged images. Bars and horizontal lines indicate means and standard deviations. *P<0.01, **P<0.001.

Figure 5. Changes in the circumferential-strain (ΔC-strain) among ischemic, non-ischemic, infarcted, and control segments. Bars and horizontal lines indicate means and standard deviations. *P<0.001.

Figure 6. Absolute circumferential-strain (C-strain) differences between stressed and at-rest tagged images. Bars and horizontal lines indicate means and standard deviations. *P<0.01, **P<0.001.
In contrast, segments with ischemia or infarction showed absolute C-strain values that tended to decrease under ATP-stress conditions. These observations suggest that ATP-stress conditions induced contractile impairment in segments with ischemia or infarction, with a reversed effect in non-ischemic or control segments. In addition, the at-rest C-strain values did not differ between non-ischemic and ischemic segments, whereas the absolute C-strain values under ATP-stress conditions were significantly lower in ischemic segments than in non-ischemic segments. A decrease in the stress C-strain values was an indicator of the abnormal myocardial movement that differentiates ischemic segments from non-ischemic segments.

In patients with significant stenosis, ATP may induce ischemia, resulting in coronary steal through collateral vessels. The coronary steal phenomenon causes transient ischemia or myocardial stunning. The progression of myocardial ischemia occurs in a waveform pattern, initiated at the subendocardium and extending in a gradient to the epicardial layer. The subendocardium is often the earliest myocardial layer affected by ischemia. We speculate that myocardial stunning, induced by ATP-stress, may be the cause of reduced subendocardial C-strain in ischemic segments. In addition, a significantly decreased C-strain value under at-rest conditions was a characteristic finding of infarcted segments, and seemed to be influenced by myocardial fibrosis in the infarct area and the resulting reduced myocardial torsion.

The absolute C-strain value was significantly lower in non-ischemic segments than in control segments both under ATP-stress and at-rest conditions. This result may be affected by age-related impaired systolic strain because the mean age in the present study was 61 years in the patient group vs. 28 years for the controls. However, ΔC-strain did not differ significantly between control and non-ischemic segments, which suggests that ΔC-strain has potential diagnostic utility for detecting myocardial ischemia without being influenced by variations in patients’ ages. We believe that the ΔC-strain has a higher diagnostic capability than does the stress C-strain, but there was little difference between them. We speculate that the limited number of segments with ischemia or infarction in the present study might be an important factor responsible for this finding.

Echocardiography is a simple and useful test for detecting wall motion abnormality. Recently, myocardial strain has also been measured by speckle tracking echocardiography, which is a unique echocardiographic imaging technique that analyzes motion within an ultrasonic window by tracking interference patterns and natural acoustic reflections. However, echocardiography can not generate completely circular, short-axial images for the measurement of strain in all patients, because of variations in the echo window and cardiac position among patients. CMR has the advantages of greater consistency and reproducibility than echocardiography.

Advantage of 3T MRI

Recent CMR studies have shown the advantage of performing the imaging at higher field strengths; imaging using a 3-T instrument was also shown to be superior to imaging at 1.5-T, with regard to the signal to noise ratio and for the detection of CAD. The T1 relaxation time is longer for 3-T than for 1.5-T, so the tagging grid persisted throughout the entire cardiac cycle when using 3-T. Visualization of the tagging grid in the low-noise 3-T environment was superior to that in a 1.5-T environment. Analysis of 3-T tagged CMR was shown to be able to noninvasively quantify the predominant impairment of subendocardial strain in patients with severe CAD. Subendocardial C-strain has potential as a sensitive index for the detection of significant stenotic coronary segments with a diagnostic capability equal to stress/rest SPECT. Initial experimental data obtained using myocardial layer-specific speckle tracking echocardiography have been recently reported. Currently, the development of a noninvasive technique for assessing transmural layer strain using echocardiography and tagged MRI is expected.

Study Limitations

First, the number of patients involved was small. Multiple...
comparisons should be interpreted with caution given the small sample size. Second, the mixture of ischemic, infarct, and non-ischemic myocardium in a single segment could affect the results. Third, in patients with CAD, the subendocardial longitudinal myofiber is vulnerable and susceptible in the areas of myocardial hyperperfusion; thus, it is prone to earlier damage leading to impaired longitudinal function. Because of limitations in the longitudinal tagged CMR scan, longitudinal myocardial strain was not calculated in our analysis. Finally, conventional coronary angiography was not performed to confirm ischemic and infarcted segments or coronary artery stenosis. However, previous study has reported stress perfusion-CMR as a valuable alternative to SPECT for CAD detection, with equal or better performance than SPECT in this regard.

We believe that ATP-stress perfusion-MR provides a diagnosis for ischemic segments comparable to that using conventional coronary angiography.

Conclusion

In conclusion, C-strain analysis (ie, quantitative analysis of ATP-stress tagged MR) showed contractile impairment in non-ischemic, ischemic, and infarcted segments in patients with suspected CAD. Under ATP stress, a greater decrease in C-strain was a candidate factor for differentiating ischemic segments from non-ischemic segments. A significantly decreased C-strain value at rest was useful for differentiating infarcted segments from ischemic segments.

Disclosures

Michinobu Nagao: Bayer Healthcare Japan, Modest, Research Grant; Philips Electronics Japan, Modest, Research Grant.

References