Detection of Myocardial Ischemia by $^{31}$P Magnetic Resonance Spectroscopy During Handgrip Exercise

Takahiro Yabe, MD; Kenichi Mitsunami, MD; Mamoru Okada, MD; Shigehiro Morikawa, MD; Toshiro Inubushi, PhD; Masahiko Kinoshita, MD

**Background** The metabolic changes of myocardial ischemia in patients with coronary artery disease assessed by $^{31}$P magnetic resonance spectroscopy (MRS) have been reported previously. A significant decrease in the ratio of phosphocreatine (PCr) to ATP during handgrip exercise in a group of patients with severe coronary artery disease has been demonstrated. However, there are no reports at present that directly compare cardiac $^{31}$P MRS data with exercise $^{201}$TI myocardial scintigraphy, now established as one of the most important clinical methods to assess myocardial ischemia. The purpose of this study was to investigate whether $^{31}$P MRS with handgrip exercise testing is able to detect myocardial ischemia, demonstrated by exercise $^{201}$TI scintigraphy.

**Methods and Results** Twenty-seven patients with severe stenosis of the left anterior descending coronary artery ($\geq 75\%$) and 11 normal control subjects composed the present study. Patients were divided into two groups on the basis of exercise $^{201}$TI scintigraphy: a reversible $^{201}$TI defect group (RD$[+]$) who demonstrated redistribution at the late image and a fixed $^{201}$TI defect group (RD$[−]$). While lying supine within the magnet, subjects performed handgrip exercise at 30% of maximal force once in every two cardiac cycles. $^{31}$P MR spectra were collected before and during handgrip exercise. Data were corrected for the saturation factor. ANOVA revealed significant differences among the three groups with respect to the mean±SD PCr/ATP ratio at rest (control, 1.85±0.28 $>$ RD$[+]$, 1.60±0.19 $>$ RD$[−]$, 1.24±0.30; $P<.05$). The PCr/ATP ratio decreased significantly from 1.60±0.19 at rest to 0.96±0.28 during exercise ($P<.001$) in the RD$[+]$ group ($n=15$). However, in the RD$[−]$ group ($n=12$), the ratio did not change significantly during handgrip exercise (1.24±0.30 at rest versus 1.19±0.28 during exercise). Similarly, the ratio did not change in the control group ($n=11$) (1.85±0.28 at rest versus 1.90±0.23 during exercise).

**Conclusions** Contrary to normal subjects or patients with fixed thallium defects, the PCr/ATP ratio was significantly altered by exercise in patients with reversible thallium defects. These results suggest that $^{31}$P MRS with handgrip exercise testing is a sensitive method for detecting myocardial ischemia.

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**Key Words**: magnetic resonance imaging • spectroscopy • exercise • stress • myocardium

Myocardial ischemia has been detected by various methods, such as exercise-induced ECG changes, $^{1,2}$ exercise $^{201}$TI scintigraphy, $^{3-10}$ and positron emission tomography (PET) using $[^{15}$N]$\text{ammonia}$ and/or $^{31}$P-2-fluoro-2-deoxyglucose.$^{11-14}$ At present, exercise $^{201}$TI imaging is particularly well established as a method for assessing regional myocardial perfusion in patients with coronary artery disease. $^{31}$P magnetic resonance spectroscopy (MRS) has also recently been demonstrated to be an important technique for studying the effects of ischemia on myocardial metabolism.$^{17}$

Weiss et al.$^{17}$ have reported that $^{31}$P MRS using one-dimensional chemical shift imaging during isometric handgrip exercise testing is useful in assessing the effects of ischemia on myocardial metabolism of high-energy phosphates and for evaluating responses to revascularization therapy. They have observed a significant decrease in the ratio of subendocardial phosphocreatine (PCr) to ATP during handgrip exercise in a group of patients with severe coronary artery disease (CAD). No changes, however, were noted in PCr/ATP ratios in normal subjects and cardiac patients with nonischemic heart disease during exercise.

The main purpose of this study was to investigate whether $^{31}$P MRS with dynamic handgrip stress testing, compared with exercise $^{201}$TI scintigraphy, could serve as a useful tool for detecting myocardial ischemia. Patients with severe stenosis of the left anterior descending coronary artery (LAD) were divided into two groups on the basis of exercise $^{201}$TI scintigraphy results: a reversible $^{201}$TI defect group and a fixed $^{201}$TI defect group. $^{31}$P MRS with handgrip exercise testing was then performed on all patients and normal subjects.

**Methods**

**Subjects**

Twenty-seven patients with severe stenosis ($\geq 75\%$) of the LAD and 11 healthy volunteers with no clinical evidence of cardiac disease composed the present study. Coronary angiograms were analyzed by two independent, blinded, experienced angiographers. Luminal diameter stenosis was measured by videodensitometry using a Vanguard Coronary Analyzer System (Vanguard Instrument Corp, Melville, NY).

Patients were divided into two groups on the basis of exercise $^{201}$TI scintigraphy results using 3-hour postexercise single-photon emission computed tomography (SPECT) imaging (Table I). The reversible $^{201}$TI defect group (RD$[+]$) consisted of 11 men and 4 women 43 to 74 years old (mean±SD, 62±8 years). The
TABLE 1. Coronary Angiography and 99mTc Radionuclide Ventriculography Data for Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex</th>
<th>Stenosis</th>
<th>LVEF, %</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD(+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50/M</td>
<td>90%LAD, 90%RCA</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>74/F</td>
<td>75%LAD, 90%LCx, 75%RCA</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>68/M</td>
<td>75%LAD, 55%LCx</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>67/M</td>
<td>75%LAD, 100%LCx</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>65/M</td>
<td>90%LAD, 75%LCx</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>90%LAD</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>61/F</td>
<td>99%LAD, 75%LCx</td>
<td>70</td>
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<td>8</td>
<td>67/M</td>
<td>99%LAD, 75%LCx</td>
<td>73</td>
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<td>9</td>
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<td>90%LAD</td>
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<td>65/F</td>
<td>80%LAD, 90%LCx, 99%RCA</td>
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</tr>
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<td>69/M</td>
<td>75%LAD, 50%LCx, 100%RCA</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RD(−)</td>
<td></td>
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<tr>
<td>1</td>
<td>62/M</td>
<td>60%MRT, 100%LAD, 90%LCx, 25%RCA</td>
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<tr>
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<td>63/F</td>
<td>25%MRT, 99%delay LAD</td>
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<td>55/M</td>
<td>100%LAD, 25%RCA</td>
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<td>100%LAD</td>
<td>48</td>
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<td>100%LAD</td>
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<td>63/M</td>
<td>100%LAD, 75%LCx</td>
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<tr>
<td>11</td>
<td>50/M</td>
<td>100%LAD</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>70/F</td>
<td>100%LAD</td>
<td></td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction by 99mTc radionuclide ventriculography; RD(+) reversible 201TI defect group; RD(−), fixed 201TI defect group; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery; and LMT, left main trunk coronary artery.

fixed 201TI defect group (RD(−)) consisted of 9 men and 3 women; 26 to 68 years old (mean±SD, 39±14 years). All subjects in the control group were free of any previous clinical history of heart disease. Informed consent was obtained from all subjects.

Exercise 201TI Imaging

Exercise 201TI imaging was performed within 1 month of the MRS study. There were no significant clinical events (acute myocardial infarction or unstable angina) intervening between the exercise test and the MRS study. All patients underwent multistage treadmill exercise testing according to the Bruce protocol. Heart rate, blood pressure, and 12-lead ECG were monitored during exercise. Incremental exercise testing was continued until the onset of either anginal chest pain, ST-segment depression of ≥2 mm, fatigue, or target heart rate. At peak exercise, a dose of 111 MBq of 201TI was injected intravenously, after which exercise was continued for an additional 30 seconds. SPECT imaging was obtained within 3 minutes after the cessation of exercise and was repeated 3 hours later. Images were acquired with a large field of view rotating gamma camera (GCA-901, Toshiba Medical, Tokyo) equipped with a low-energy, general-purpose collimator interfaced to a dedicated computer (GMS-550U, Toshiba Medical). Early and delayed (3 hours later) 201TI images were obtained over a 180° arc (32 images per study; 40 seconds per image), spanning from a 45° right anterior oblique to a 45° left posterior oblique view.

31P MRS

31P MR experiments were performed with a 1.5-T, 1-m-bore, whole-body MR imaging system (Signa; General Electric Medical Systems, Milwaukee, Wis). A home-built, compact, circular, 31P double-tuned surface coil was initially placed over the anterior chest wall with the subject in the supine position. Conventional 1H MR imaging was performed before 31P MRS to confirm and guide the placement of the surface coil over the anteroseptal region of the left ventricle (Fig 1). Subjects were kept in a constant position on the table during the acquisition of 31P MRS data, and the table was maintained at an established center position during the acquisitions.

MR spectra were spatially localized with depth-resolved surface coil spectroscopy (DRESS). The slice thickness was 25 mm, and the slice was positioned so that much of it was filled by the anterior myocardium. Before each measurement, shimming on the proton signal of water in the region of interest was performed. The typical line width was between 0.3 and 0.6 ppm. Each spectrum represented an average of 256 free induction decays, which were acquired during every other heartbeat at end systole (350 milliseconds after the R wave of the ECG). The radio frequency pulse power was kept constant for all subjects. Subjects lay supine and performed handgrip exercises once in every two cardiac cycles with 30% of maximal force. MR spectra were collected before and during the handgrip exercise. The acquisition time ranged from 7 to 8 minutes per set of spectra before or during the exercise. The total MR examination time ranged from 45 to 60 minutes.

The integrated areas of the resonances of PCR and beta-phosphates of ATP (β-ATP) were measured after a 10-Hz line-broadening exponential filter was applied and the peaks were fitted to an 80% gaussian and a 20% lorezian line with a GEN-1280 data processing station (General Electric, Fremont, Calif). The areas were corrected for partial saturation at pulse conditions that were determined by the following formula19,20:

\[
SF = \left[1 - \exp\left(-TR/T_{1}\right)\right] \cdot \sin \alpha / \left[1 - \exp\left(-TR/T_{1}\right) \cdot \cos \alpha \right]
\]

where SF is saturation factor, TR is repetition time, T1 is spin-lattice relaxation time, and \(\alpha\) is flip angle.

The flip angles for the subjects were estimated by use of a phantom that yielded the same Q factor as the subjects. The T1...
values of cardiac PCr and β-ATP were estimated from the spectra of four healthy volunteers acquired at TRs of 1, 2, 3, and 15 seconds with no ECG gating. The T1 values of PCr and β-ATP were 4.18 and 1.70 seconds, respectively. The saturation factor for the heart rate was calculated by use of the same flip angle and the same T1 value for all the subjects. This correction assumes that normal and infarcted myocardium have the same spin-lattice relaxation times.

The ratio of PCr to ATP was derived from the integrated areas of the resonances of PCr and the β-phosphate of ATP. Levels of ATP were represented by the β-ATP, since the β-phosphate of ATP does not overlap with resonances of other compounds. Contamination of blood ATP from the section intersecting the ventricular cavity was corrected by subtraction of a blood ATP signal corresponding to 15% of the total integrated 2,3-diphosphoglycerate signal from the β-ATP signal.

Exercise Protocol

While lying supine within the magnet, all subjects in the study were required to perform bilateral handgrip once every two cardiac cycles with 30% maximal force. The force was monitored by a home-built nonmagnetic dynamometer and was observed continuously by an investigator. The systolic blood pressure was measured before and during exercise by the nonmagnetic cuff method at the popliteal fossa of the leg. 31P MR spectra were collected before and during the 7- to 8-minute period of handgrip exercise. Spectral acquisition commenced 1 to 2 minutes after exercise began.

**Statistical Analysis**

Data are presented as mean±SD. The differences in LVEF (%) between the two groups (RD[+] and RD[−]) were assessed by an unpaired t test. Scheffé’s F test for multiple contrasts was applied to detect significant differences as defined by ANOVA among the three groups (RD[+], RD[−] and control subjects). Changes before and during exercise were analyzed by means of paired Student’s t test. A probability value of P<.05 was considered to be significant.

**Results**

Table 2 shows hemodynamic and PCr/ATP ratio data at rest and during exercise. The results of the one-way ANOVA demonstrated that subjects in the RD(−) group had significantly lower myocardial PCr/ATP ratios at rest than those in the RD(+) (P<.05) and control (P<.01) groups. In addition, subjects in the RD(+) group had lower ratios than the control group (P<.05) (Fig 2).

During exercise, the heart rate increased from 68±12 beats per minute (mean±SD) at rest to 75±13 beats per

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**Table 2.** Hemodynamic and PCr/ATP Ratio Data at Rest and During Exercise

<table>
<thead>
<tr>
<th></th>
<th>HR, bpm</th>
<th>BP, mm Hg</th>
<th>DP, mm Hg · bpm</th>
<th>PCr/ATP(1)</th>
<th>PCr/ATP(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD(+) (n=15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>68±12</td>
<td>118±13</td>
<td>8221±1900</td>
<td>1.56±0.19</td>
<td>1.60±0.19</td>
</tr>
<tr>
<td>Exercise</td>
<td>75±13*</td>
<td>134±16*</td>
<td>10 352±2539*</td>
<td>0.94±0.27†</td>
<td>0.96±0.28†</td>
</tr>
<tr>
<td>RD(−) (n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>63±11</td>
<td>115±14</td>
<td>7092±975</td>
<td>1.18±0.28</td>
<td>1.24±0.30</td>
</tr>
<tr>
<td>Exercise</td>
<td>74±13*</td>
<td>128±13*</td>
<td>9428±1665*</td>
<td>1.12±0.24</td>
<td>1.19±0.28</td>
</tr>
<tr>
<td>Control (n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>67±8</td>
<td>117±12</td>
<td>7901±1468</td>
<td>1.80±0.28</td>
<td>1.85±0.28</td>
</tr>
<tr>
<td>Exercise</td>
<td>77±11*</td>
<td>131±13*</td>
<td>10 124±2147*</td>
<td>1.84±0.26</td>
<td>1.90±0.23</td>
</tr>
</tbody>
</table>

PCr indicates phosphocreatine; HR, heart rate; bpm, beats per minute; BP, blood pressure; DP, double product; PCr/ATP(1), PCr/ATP ratios without blood ATP correction; PCr/ATP(2), PCr/ATP ratios with blood ATP correction; RD(+), reversible 201TI defect group; and RD(−), fixed 201TI defect group. Data are presented as mean±SD. Changes at rest and during exercise were analyzed by means of Student’s t test. *P<.01 vs at rest; †P<.001 vs at rest.
minute in the RD(+) group, from 63±11 to 74±13 beats per minute in the RD(−) group, and from 67±8 to 77±11 beats per minute in the control group. There was no significant difference in heart rate among the three groups. The mean resting double product (heart rate times blood pressure) was 8221±1900 mm Hg times beats per minute in the RD(+) group, 7092±975 mm Hg times beats per minute in the RD(−) group, and 7901±1468 mm Hg times beats per minute in the control group. The double product increased during exercise to mean peak values of 10 352±2539, 9428±1665, and 10 124±2147 mm Hg times beats per minute, respectively. No significant differences existed among the three groups in the values obtained at rest or during exercise. Two patients in the RD(+) group developed chest pain during exercise. In the RD(−) group, one patient experienced chest pain and four others developed dyspnea during exercise.

The 31P MR spectra from the anterior left ventricle before and during exercise in a typical RD(+) patient are shown in Fig. 3. This patient, a 50-year-old man, had typical anginal pain on exertion. Coronary angiography demonstrated 90% stenosis of the LAD and 90% stenosis of the right coronary artery (RCA). 99mTc radionuclide ventriculography revealed a normal LVEF of 66%. The PCr/ATP ratio decreased from 1.51 at rest to 1.06 during exercise. The patient experienced anterior chest pain during exercise. As shown in Fig. 4, the mean PCr/ATP ratio in the RD(+) group (n=15) before exercise was 1.60±0.19 and fell significantly (by 40%) during exercise, to 0.96±0.28 (P<.001)

The 31P MR spectra of a typical patient in the RD(−) group are shown in Fig. 5. The patient was a 62-year-old man who had evidence of 60% stenosis in the left main trunk artery, total occlusion of the LAD, 75% stenosis in the left circumflex artery, and 25% narrowing of the RCA. Left ventriculogram showed anterolateral wall akinesis and apical dyskinesis. 99mTc radionuclide ventriculography revealed a low LVEF of 18%, and exercise 201Tl imaging demonstrated extensive areas of fixed perfusion defects within the anteroseptal wall. The PCr/ATP ratio did not change significantly with exercise (1.03 at rest versus 1.04 during exercise). In the RD(−) group (n=12), the mean ratios did not change significantly during exercise (1.24±0.30 at rest versus 1.19±0.28 during exercise) (Fig 6).

Fig. 7 shows typical 31P MR spectra of a subject in the control group. The subject, a 27-year-old man, was a healthy volunteer with no previous clinical evidence of cardiac disease. The ratio was not altered by exercise

![Fig 2. Plot showing phosphocreatine (PCr)/ATP ratios at rest in reversible 201Tl defect (RD[+]), fixed 201Tl defect (RD[−]), and control (C) groups. ANOVA revealed significant differences among the three groups (control, 1.85±0.28>RD(+), 1.60±0.19>RD(−), 1.24±0.30).](image)

![Fig 3. Representative cardiac 31P magnetic resonance spectroscopy spectra from a patient in the RD(+) group at rest and during exercise. The PCr/ATP ratio decreased from 1.51 at rest to 1.06 during exercise. RD(+) indicates reversible 201Tl defect group (3-hour postexercise single-photon emission computed tomography images); PCr, phosphocreatine; PME, phosphomonoesters; Pi, inorganic phosphate; and PDE, phosphodiesterases.](image)

![Fig 4. Graph showing changes in phosphocreatine (PCr)/ATP ratio in response to handgrip exercise in reversible 201Tl defect (RD[+]) group patients. The mean±SD ratio before exercise was 1.60±0.19 and fell significantly during exercise to 0.96±0.28 (P<.001).](image)
The diagnosis of myocardial ischemia is based on the presence of either subjective symptoms, including angina, or objective signs such as ECG changes. Myocardial ischemia has also been detected noninvasively by various methods, including exercise ECG, ambulatory Holter monitoring, echocardiography, cine MR imaging, exercise $^{201}$TI SPECT, and PET using [15N]ammonia and/or $^{18}$F-2-fluoro-2-deoxyglucose. At present, MRS has also been established as an important technique for studying the effects of ischemia on myocardial metabolism. Before the development of MRS, assessment of myocardial biochemical alterations associated with ischemia was limited to the analysis of biopsy specimens or indirect analysis by coronary sinus blood sampling for compounds such as lactate and succi-

**Discussion**

The diagnosis of myocardial ischemia is based on the presence of either subjective symptoms, including angina, or objective signs such as ECG changes. Myocardial ischemia has also been detected noninvasively by various methods, including exercise ECG, ambulatory Holter monitoring, echocardiography, cine MR imaging, exercise $^{201}$TI SPECT, and PET using [15N]ammonia and/or $^{18}$F-2-fluoro-2-deoxyglucose. At present, MRS has also been established as an important technique for studying the effects of ischemia on myocardial metabolism. Before the development of MRS, assessment of myocardial biochemical alterations associated with ischemia was limited to the analysis of biopsy specimens or indirect analysis by coronary sinus blood sampling for compounds such as lactate and succi-

**Fig. 5.** Representative cardiac $^{31}$P magnetic resonance spectroscopy spectra from a patient in the RD(−) group at rest and during exercise. The phosphocreatine (PCr)/ATP ratio did not change significantly during exercise (1.03 at rest vs 1.04 during exercise). RD(−) indicates fixed $^{201}$TI defect group (3-hour post-exercise single-photon emission computed tomography images); PME, phosphomonoesters; Pi, inorganic phosphate; and PDE, phosphodiesterase.

(2.33 at rest versus 2.41 during exercise). The mean ratio similarly did not change significantly in the control group (n=11) (1.85±0.28 at rest versus 1.90±0.23 during exercise) (Fig 8). No correlation was noted between age or sex and the PCr/ATP ratio at rest or during exercise.

**Fig. 6.** Graph showing changes in phosphocreatine (PCr)/ATP ratio in response to handgrip exercise in fixed $^{201}$TI defect (RD[−]) group patients. The mean±SD ratio did not change significantly during exercise (1.24±0.30 at rest vs 1.19±0.28 during exercise).

**Fig. 7.** Representative cardiac $^{31}$P magnetic resonance spectroscopy spectra from a subject in the normal control (C) group at rest and during exercise. The phosphocreatine (PCr)/ATP ratio did not change significantly during exercise (2.33 at rest vs 2.41 during exercise). PME indicates phosphomonoesters; Pi, inorganic phosphate; and PDE, phosphodiesterase.

**Fig. 8.** Graph showing changes in phosphocreatine (PCr)/ATP ratio in response to handgrip exercise in the normal control (C) group subjects. The mean±SD ratio did not change significantly during exercise (1.85±0.28 at rest vs 1.90±0.23 during exercise).
The development of MRS has made it possible to directly measure metabolically important compounds in a noninvasive method.

MRS research concerning human ischemic heart disease has been limited to only a few preliminary studies. The calculation of ratios of PCr to inorganic phosphate (P_i), shown previously to be a sensitive marker for ischemia, is difficult to perform in humans because of contamination of the cavity blood. Accordingly, only PCr/ATP ratios were measured in this study by the DRESS method.

The ratios obtained for normal control subjects in our study are comparable to results reported by other groups. \( ^{17,26,31-34} \) We demonstrated that subjects in the RD(−) group had lower myocardial PCr/ATP ratios at rest than those in both the RD(+) and control groups and that subjects in the RD(+) group had lower ratios than those in the control group. In addition, the LVEF was significantly lower in the RD(−) group relative to the RD(+) group as determined by \(^{99m} \text{Tc} \) radionuclide ventriculography. These results suggest that the degree of CAD is inversely proportional to the PCr/ATP ratio. Since myocardial scar tissue presumably contains little or almost no ATP, the acquired signal in the RD(−) group probably came from the residual myocardium, which has to compensate for the scarred tissue to maintain adequate global left ventricular function. Weiss et al.\(^ {17} \) have reported that the resting PCr/ATP ratio was slightly lower in patients with coronary heart disease than in control subjects and in patients with nonischemic heart disease. Hardy et al.\(^ {32} \) found that reduced PCr/ATP ratios in patients with congestive heart failure resulted from severe multivessel CAD. Our results are in agreement with the findings from these studies.

Our investigations also revealed that the PCr/ATP ratio decreased significantly during exercise in the RD(+) group. This ratio, however, failed to change significantly during exercise in both the RD(−) and control groups. This is consistent with the findings of Weiss et al.\(^ {17} \) who demonstrated that PCr/ATP ratios in patients with severe CAD decreased from 1.45±0.31 at rest to 0.91±0.24 during isometric handgrip exercise \((P<.001)\) and then recovered to 1.27±0.38 2 minutes after exercise. In normal subjects, the mean ratio of PCr/ATP with exercise remained unchanged \((1.72±0.15, 1.74±0.17, \text{and } 1.77±0.16 \text{ before, during, and after exercise, respectively). In addition, they demonstrated a resolution of exercise-induced metabolic abnormalities in certain patients after revascularization.}

In the RD(+) group in our study, the decrease in the mean PCr/ATP ratio observed during exercise was probably secondary to a restriction of myocardial oxygen delivery as a result of CAD to such an extent that a transient excess consumption of high-energy metabolites occurred. With stress, however, ischemia causes reduced systolic thickening. Therefore, there is a possibility that the MRS study will detect less PCr (because of a reduced volume of myocardium in the region of interest) and more blood ATP in cases with evoked ischemia. Thus, results with stress may not be “metabolic” (ie, reduced PCr/ATP in the myocyte) but an artifact of the localization scheme and relatively large voxels. When we compared PCr/ATP ratio data with blood ATP correction with uncorrected data, results revealed the same trend (Table 2). In view of the above, we believe that the results may be mainly metabolic.

The PCr/ATP ratio in the RD(−) group did not change significantly during exercise. This finding suggests that the imbalance between oxygen supply and demand cannot be provoked by exercise in the RD(−) group, since no significant mass of viable ischemic myocardium exists. The PCr/ATP ratio in the control group also did not change significantly during exercise. In the absence of severe reductions of coronary flow, the heart can regulate and maintain high-energy phosphate levels over a range of workloads applied in this study.

We used exercise \(^{201} \text{Tl} \) SPECT imaging as an index of myocardial ischemia in patients with CAD. To the best of our knowledge, this is the first report using exercise testing with \(^{201} \text{Tl} \) scintigraphy in concert with MRS to divide CAD patients into two groups, RD(+) and RD(−).

Exercise \(^{201} \text{Tl} \) scintigraphy has also been used to assess myocardial viability in patients with CAD.\(^ {3} \) Reversible \(^{201} \text{Tl} \) defects are associated with viable ischemic myocardium, whereas fixed \(^{201} \text{Tl} \) defects have come to be regarded as representing nonviable infarcted regions. However, recent studies have demonstrated that fixed \(^{201} \text{Tl} \) defects observed on 4-hour postexercise planar images can become reversible when patients are reimaged at 24 hours after exercise.\(^ {4-6} \) Additionally, fixed \(^{201} \text{Tl} \) defects have been reported to disappear after revascularization.\(^ {7,8} \)

Recently, it was shown that viable myocytes that are subject to ischemia may show prolonged alterations in function, even after reperfusion. This phenomenon of viable myocytes demonstrating relatively prolonged abnormalities in contractile function has become known as stunned or hibernating myocardium.\(^ {35,37} \) Thus, it is possible that there may have been certain patients with both necrotic and injured but still viable myocardium in our RD(−) group. In the future, MRS may possess the ability to adequately differentiate conditions in which perfusion is abnormal but no evidence of ischemia exists (hibernating myocardium).\(^ {38} \)

Our study demonstrates that MRS is capable of detecting stress-induced metabolic abnormalities in patients with CAD. Several prior studies have demonstrated that routine exercise testing greatly enhances the sensitivity for detecting diseased myocardium.\(^ {17,25,30} \) We performed bilateral dynamic handgrip exercise to induce ischemia. In general, ischemic responses are less frequently noted with static and static-dynamic effort than with symptom-limited dynamic exercise testing.\(^ {40-43} \)

Our data were similar to those noted by Weiss et al.\(^ {17} \) regarding measurements of heart rate, blood pressure, and double product before and during exercise. The rate-pressure product achieved during our exercise stress was less than that achieved with other exercise testing such as treadmill or bicycle ergometer stress tests. Our method, which is safe and simple and also avoids large thoracic movement, appears to be a favorable exercise technique during MR imaging.

Recently, intravenous dobutamine has also been used effectively to elicit myocardial ischemia, with abnormalities in high-energy phosphates observed in patients studied with MRS.\(^ {38} \) Further evolution of MRS local-
organization techniques and stress methodologies will most certainly improve the efficacy of MRS.

Study Limitations

The DRESS localization technique was applied to subjects in our study. This technique was developed by Bottomley et al. for surface-coil experiments and represents an effective, one-dimensional approach to localization. Localized human in vivo spectra of metabolites are almost invariably acquired under conditions of partial saturation to optimize the signal-to-noise ratio per unit time. In addition, the DRESS technique requires delays of approximately 1.5 milliseconds between the center of the excitation pulse and the commencement of data acquisition to achieve spatial encoding. Variability in saturation conditions and/or acquisition delays are likely major sources of systematic error. MR spectra obtained were corrected for the saturation factor, which was calculated on the assumption that the heart T1 values of phosphorus metabolites in all subjects were the same in this study. The effects of aging and various heart diseases on T1 values of cardiac phosphorus metabolites should be examined in future studies.

The ability of this technique to successfully confine data acquisition to a specified region is crucial for the success of cardiac spectroscopy because contamination by skeletal muscle will falsely elevate the PCr peak (since skeletal muscle has a higher PCr concentration than myocardium). Furthermore, inclusion of chamber blood in the volume will mask or falsely elevate the P1 resonance by signals from 2,3-diphosphoglycerate. 

Conclusions

31P MRS with dynamic handgrip exercise testing was performed in patients with CAD (RD[+]) and RD[−]) and normal control subjects. Patients with fixed perfusion defects by thallium scintigraphy had lower myocardial PCr/ATP ratios at rest relative to patients with reversible defects (P < 0.05) or control subjects (P < 0.01). In addition, patients with reversible defects had lower ratios than control patients (P < 0.05). During exercise, the PCr/ATP ratio decreased significantly in patients with reversible perfusion defects. This ratio did not change significantly during exercise, however, either in the control group or in patients with fixed perfusion defects. These findings suggest that 31P MRS with exercise testing is a sensitive method for the detection of myocardial ischemia.

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Detection of myocardial ischemia by 31P magnetic resonance spectroscopy during handgrip exercise.
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