Dobutamine Cardiovascular Magnetic Resonance for the Detection of Myocardial Ischemia With the Use of Myocardial Tagging

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Background—The purpose of this study was to assess the value of high-dose dobutamine cardiovascular magnetic resonance (CMR) with myocardial tagging for the detection of wall motion abnormalities as a measure of myocardial ischemia in patients with known or suspected coronary artery disease.

Methods and Results—Two hundred eleven consecutive patients with chest pain underwent dobutamine-CMR 4 days after antianginal medication was stopped. Dobutamine-CMR was performed at rest and during increasing doses of dobutamine. Cine-images were acquired during breath-hold with and without myocardial tagging at 3 short-axis levels. Regional wall motion was assessed in a 16-segment short-axis model. Patients with new wall motion abnormalities (NWMA) were examined by coronary angiography. Dobutamine-CMR was successfully performed in 194 patients. Dobutamine-CMR without tagging detected NWMA in 58 patients, whereas NWMA were detected in 68 patients with tagging (P=0.002, McNemar). Coronary angiography showed coronary artery disease in 65 (96%) of these 68 patients. All but 3 of the 65 patients needed revascularization. In the 112 patients with a negative dobutamine-CMR study, without baseline wall motion abnormalities, the cardiovascular occurrence-free survival rate was 98.2% during the mean follow-up period of 17.3 months (range, 7 to 31).

Conclusions—Dobutamine-CMR with myocardial tagging detected more NWMA compared with dobutamine-CMR without tagging and reliably separated patients with a normal life expectancy from those at increased risk of major adverse cardiac events. (Circulation. 2003;107:1592-1597.)

Key Words: magnetic resonance imaging myocardium stress ischemia

Myocardial tagging allows determination and quantification of left ventricular wall thickening of specific myocardial segments.1-3 Myocardial tagging was first used in combination with low-dose dobutamine cardiovascular magnetic resonance (CMR) for the assessment of myocardial viability.4,5 High-dose dobutamine-CMR (up to 40 μg/kg per minute) has been useful for the detection of myocardial ischemia.6,7 The cine-CMR technique allows accurate delineation of the endocardium and epicardium and offers a reproducible assessment of left ventricular wall thickening.8 Reduction of myocardial circumferential shortening and systolic wall thickening are sensitive parameters for the detection of myocardial ischemia.3,9 The addition of myocardial tagging to dobutamine-CMR may further enhance diagnostic accuracy.1 Without tagging, ventricular contraction is evaluated by the movement of the endocardial and epicardial boundaries. With tagging, extra visual markers are created within the myocardium, which move with the movements of the myocardial wall. This facilitates the assessment of its contractile behavior.

The purpose of the present study was to assess the value of high-dose dobutamine-CMR with myocardial tagging for the determination and evaluation of myocardial ischemia in patients presenting with chest pain.

Methods

Study Population

The study population consisted of 211 consecutive patients with chest pain referred for diagnosis of myocardial ischemia regardless of known coronary artery disease (CAD). The patients were recruited from the outpatient clinic of the Department of Cardiology. All patients had an inconclusive diagnosis of myocardial ischemia by means of history, ECG-recording at rest, and if performed during bicycle exercise test. Dobutamine stress echocardiography (DSE) or perfusion scintigraphy was not performed. The outcome of the dobutamine-CMR study was used as an arbiter to decide about coronary angiography (CAG). Patients with an acute coronary
syndrome, atrial fibrillation, severe arterial hypertension (>220/120 mm Hg), CMR-incompatible metallic implants, or known claustrophobia were excluded.

Eighty-three patients had a previous myocardial infarction, and 49 patients had undergone revascularization procedures (25, PTCA; 19, CABG; 5 patients, both procedures). To ensure myocardial response to dobutamine, all antianginal medication was stopped 4 days before the CMR examination. The Medical Ethics Committee approved the study protocol. All subjects gave informed consent.

MR Study
After the patient was positioned on the MR scanning table, an intravenous access was established through an antecubital vein. ECG monitoring leads, a phased-array surface coil covering the heart, and a brachial blood pressure cuff were applied.

A single-lead ECG was continuously monitored. Systolic and diastolic blood pressures were recorded with an automatic device (Welch-Allyn, Emro-medical) at baseline and every 3 minutes throughout the procedure. After baseline acquisitions, dobutamine was infused intravenously using a digital pump injector situated outside the scanner room. In case a wall motion abnormality (WMA) was detected at baseline, infusion was started with 5 μg/kg per minute, after which the dose of dobutamine was increased to 10, 20, 30, and 40 μg/kg per minute. If no WMA was detected at baseline, we started with 10 μg/kg per minute. Imaging began 6 minutes after each dose increase and required 3 minutes per dose increase. Imaging consisted of acquiring 3 short-axis cine images (basal, midventricular, and apical) without and two short-axis cine-images (basal and midventricular) with myocardial tagging. During the infusion of dobutamine, the radiologist and cardiologist were present in the MR suite to monitor the condition of the patient and to evaluate the images directly.

Criteria for ending the dobutamine-CMR examinations were (1) development of new WMA (NWMA), (2) fall of systolic blood pressure of >40 mm Hg, (3) marked hypertension (>240/120 mm Hg), (4) severe chest pain, (5) ventricular arrhythmias, and (6) intolerable side effects of dobutamine. The total duration of the CMR study, including preparation of the patient and scan time, averaged 50 minutes (SD, 12).

MRI Technique
CMR was performed with the use of a standard 1-T MRI system (Impact-Expekt, Siemens Medical Systems, Erlangen). We used an ECG-triggered, segmented gradient-echo pulse sequence (FLASH/TR: 90 ms/TE: 6.1 ms/FOV: 256×256). The basal plane was taken 1.5 cm below the mitral valve. The midventricular and apical short-axis views were divided equally over the remaining part of the left ventricle.

Tagging was performed with a standard FLASH grid-sequence (TR: 96 ms/TE: 4.4 ms/FOV: 256×256). Nonselective radiofrequency pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients were used to achieve tag spacing of 8 mm. Each cine–breath-hold acquisition took 15 to 19 heartbeats and was made in maximum inspiration. If the heart rate reached 100 beats per minute, the number of phases per acquisition was decreased to optimize temporal resolution.

MRI Analysis
Myocardial ischemia was defined as an induced WMA in at least 2 segments at different consecutive planes of the left ventricle. Short-axis images were divided into multiple segments with 6 segments in the basal and midventricular and 4 segments in the apical image. All the images were scored by using a 4-point scale, according to the guidelines of the American Society of Echocardiography.10 Per segment, the wall motion was graded as 1=normal or hyperkinesia, 2=hypokinesia, 3=akinesia, and 4=dyskinesia. Baseline (at rest) WMA was defined as WMA in 1 or more segments.

Wall motion score index (WMSI) was derived as the mean score of all segments (n=16) of all short-axis images. WMSI data of the cine-images with and without tagging were determined from baseline and peak stress images. The WMSI data with tagging included 12 segments of basal and midventricular level with tagging and 4 segments of the apical plane without tagging.

If WMAs were already observed at rest and improved during low-dose dobutamine stress but worsened during peak stress, then these WMAs were considered diagnostic of inducible myocardial ischemia. If segments that were akinetic at rest became dyskinetic during stress, without improvement with low-dose dobutamine, this was not considered diagnostic of inducible ischemia.11

All dobutamine-CMR images were magnified (×2) and displayed as continuous cine-loops on high-resolution gray-scale monitors. The short-axis images were analyzed during and directly after the examination by two experienced investigators who interpreted the images independently. Differences in classifications were settled in a consensus review. All data were expressed as mean values ±SD; a P value of <0.05 was considered statistically significant. WMSI values were compared using a paired t test. The numbers of patients defined as having NWMA were compared between dobutamine-CMR with and without tagging by use of the McNemar test.

Patients with a negative dobutamine-CMR study were followed by an outpatient clinic 3 months after the examination. After this period, the patients were called every 3 to 6 months to assess their clinical status of major adverse cardiac events (MACE), which was defined as myocardial ischemia, myocardial infarction, heart failure, or cardiac death. The survival free of MACE was calculated by the Kaplan-Meier method and compared between groups using the log rank test.

Angiography
When NWMA were detected, the dobutamine-CMR study was followed by CAG within 3 weeks. The CAGs were documented at 12.5 images (matrix: 512×512) per second in multiple (standard) projections. Hemodynamically significant CAD was defined as a diameter reduction of >50% in one or more major epicardial coronary arteries. Immediately after the procedure, a trained observer interpreted all angiographic studies blindly and independently. Patients were classified as having 1-, 2-, or 3-vessel disease.

Results
Of the original 211 patients (Figure 1), dobutamine-CMR was successfully performed in 194 (92%). Seventeen (8%) patients could not be investigated adequately because of nausea (n=3), severe drop in systolic blood pressure (>40 mm Hg) (n=2), atrial fibrillation (n=1), breathing artifacts (n=5), claustrophobia (n=5), or because antianginal medication was not stopped in time (n=1).

Besides minor complications, one patient had ventricular fibrillation, which was successfully treated by resuscitation.

The demographic and hemodynamic data are listed in Table 1. The association between dobutamine-CMR findings and WMSI values are listed in Table 2.

No Baseline WMA
On the baseline images, no WMA was detected in 157 (81%) of 194 patients. Forty-six patients had a history of non-Q-wave myocardial infarction. When stressed with dobutamine, nontagged images showed NWMA in 37 patients (24%) (mean WMSI=1.0 at rest) and 1.35 (SD, 0.23) with dobutamine, P<0.001. Eight (5%) additional patients with NWMA were detected through the use of the tagged images (Figure 2). In 112 patients (71%), no NWMA was found.

Baseline WMA
On the baseline images, WMA was already present in 37 (19%) of 194 patients. All these patients had a history of
myocardial infarction. Without tagging, 21 patients (57%) had NWMA when stressed with dobutamine (mean WMSI 1.29, SD, 0.24) at rest and 1.71 (SD, 0.37) with dobutamine (P<0.001). The tagging technique detected 2 (5%) additional patients with NWMA. Twenty-three patients (62%) were found positive with tagging (mean WMSI 1.29, SD, 0.23) at rest, and 1.71 (SD, 0.38) with dobutamine (P<0.001), whereas no NWMAs were found in 14 patients (38%).

No NWMA and No Baseline WMA

Of the 112 patients who had no inducible myocardial ischemia and without baseline WMA, 110 (98.2%) patients were free of MACE during the follow-up period of 7 to 31 months (average, 17.3 months). Two patients (1.8%) had myocardial ischemia, which occurred more than 12 months after the examination. Both patients underwent PTCA. The Kaplan-Meier curve is presented in Figure 3. The annual MACE rate of patients without NWMA and without baseline WMA was 0.7%.

No NWMA and Baseline WMA

Fourteen patients showed baseline WMA, which did not change when stressed with dobutamine (mean WMSI=1.18, SD, 0.17). Of these 14 patients 4 (29%) showed a new MACE during follow-up. One patient had sudden death 2 months after the examination. He had sustained an extensive inferior myocardial infarction. Without tagging, 21 patients (57%) had NWMA when stressed with dobutamine (mean WMSI=1.29, SD, 0.24) at rest and 1.71 (SD, 0.37) with dobutamine (P<0.001). The tagging technique detected 2 (5%) additional patients with NWMA. Twenty-three patients (62%) were found positive with tagging (mean WMSI=1.29, SD, 0.23) at rest, and 1.71 (SD, 0.38) with dobutamine (P<0.001), whereas no NWMAs were found in 14 patients (38%).

Table 1. Demographic and Hemodynamic Data (n=194)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±12</td>
</tr>
<tr>
<td>Male, %</td>
<td>66.8</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>42.7</td>
</tr>
<tr>
<td>PTCA, %</td>
<td>15.5</td>
</tr>
<tr>
<td>CABG, %</td>
<td>12.4</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>79±13</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>85±11</td>
</tr>
<tr>
<td>Peak diastolic blood pressure, mm Hg</td>
<td>90±14</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg</td>
<td>153±28</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mm Hg</td>
<td>174±25</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>80±16</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>127±19</td>
</tr>
<tr>
<td>Rate-pressure product* at rest</td>
<td>12.345±3.711</td>
</tr>
<tr>
<td>Rate-pressure product* at peak stress</td>
<td>22.036±4.464</td>
</tr>
<tr>
<td>Maximum dose dobutamine, μg/kg per minute</td>
<td>37±6</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or percentages.

*Rate-pressure product=(heart rate) x (systolic blood pressure).

Table 2. Wall Motion Score Index Before and After High-Dose Dobutamine by Status of New Wall Motion Abnormalities

<table>
<thead>
<tr>
<th>NWMA present</th>
<th>Baseline WMSI</th>
<th>Peak WMSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontagged studies (n=58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No baseline WMA (n=37)</td>
<td>1.0</td>
<td>1.35±0.23*</td>
</tr>
<tr>
<td>Baseline WMA (n=21)</td>
<td>1.29±0.24</td>
<td>1.71±0.37*</td>
</tr>
<tr>
<td>Tagged studies (n=68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No baseline WMA (n=45)</td>
<td>1.0</td>
<td>1.35±0.16*</td>
</tr>
<tr>
<td>Baseline WMA (n=23)</td>
<td>1.29±0.23</td>
<td>1.71±0.38*</td>
</tr>
</tbody>
</table>

NWMA absent

Nontagged studies (n=136)

No baseline WMA (n=120) 1.0 1.0
Baseline WMA (n=16) 1.19±0.16 1.19±0.16
Tagged studies (n=126)

No baseline WMA (n=112) 1.0 1.0
Baseline WMA (n=14) 1.18±0.17 1.18±0.17

WMSI is expressed as mean±SD.

*P<0.001 vs baseline WMSI.

SD, 0.23) at rest, and 1.71 (SD, 0.38) with dobutamine (P<0.001), whereas no NWMAs were found in 14 patients (38%).

No NWMA and No Baseline WMA

Of the 112 patients who had no inducible myocardial ischemia and without baseline WMA, 110 (98.2%) patients were free of MACE during the follow-up period of 7 to 31 months (average, 17.3 months). Two patients (1.8%) had myocardial ischemia, which occurred more than 12 months after the examination. Both patients underwent PTCA. The Kaplan-Meier curve is presented in Figure 3. The annual MACE rate of patients without NWMA and without baseline WMA was 0.7%.

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wall infarction in the past and had heart failure. Two patients had a nonfatal myocardial infarction, which occurred more than 6 months after the study. The fourth patient had myocardial ischemia, necessitating revascularization (CABG), which occurred 18 months after the study.

**New Wall Motion Abnormalities**

Of the 194 patients, 58 (30%) patients were found positive for NWMA with matching ischemia between nontagged and tagged images (Figure 4). Of the remaining 136 patients 10 (5%) additional positive studies were detected only with the use of tagging, which is an increase of 17% (P<0.0001, McNemar).

Sixty-five (96%) of 68 patients with NWMA showed significant CAD at CAG. One-vessel disease was found in 25 patients and 2- or 3-vessel disease in 40 patients. Of the 10 patients only detected by the tagging technique, 3 had 1-vessel disease, 4 had 2-vessel disease, and 3 had 3-vessel disease. Revascularization was deemed necessary and possible in 62 (95%) patients. In 3 patients, revascularization was technically not feasible.

Three (4%) of the 68 patients showed no significant CAD at angiography, whereas both the nontagged and tagged CMR images were found positive. Two patients had a left bundle-branch block with an abnormal septal wall motion at the baseline images. In the other patient, CAG showed diffuse coronary artery irregularities without significant stenoses.

The mean maximum dose of dobutamine for detecting ischemia was 33 μg/kg per minute (SD, 8.3). The majority of the NWMA (75%) were detected at high-dose dobutamine (30 and 40 μg), whereas only 25% were detected at low-dose dobutamine (20 μg).

During the examinations, 116 of 194 (60%) of the patients had chest discomfort, but in only 60 of them (52%) myocardial ischemia was shown to be present.

**Discussion**

This is the first study that demonstrates that the use of myocardial tagging with high-dose dobutamine-CMR detects more NWMA than dobutamine-CMR studies without tagging. The results suggest that dobutamine-CMR is a specific diagnostic technique in the analysis of ischemic heart disease. Our data demonstrate that 96% of the patients with NWMA, detected by dobutamine-CMR, had significant CAD. Two other studies have reported results of dobutamine-CMR; however, no myocardial tagging was used. Nagel et al. compared dobutamine-CMR and DSE in 172 patients referred for CAG. Dobutamine-CMR provided better sensitivity (89% versus 74%) and specificity figures (86% versus 70%) for the detection of NWMA compared with DSE. However, all patients with a history of myocardial infarction had been excluded from the study. Hundley et al. reported the use of dobutamine-CMR in 139 patients who failed DSE and came up with findings similar to those of Nagel et al. In our study, 3 (4%) of 68 patients showed false-positive dobutamine-CMR findings. Two of these false judgments occurred in the beginning of our dobutamine-CMR series because of abnormal septal wall motion in left bundle-branch block.

**Figure 3.** Kaplan-Meier curves showing survival free from MACE during follow-up for negative dobutamine-CMR studies, with (dotted line) and without (black line) baseline WMA (log rank, P<0.0001).

**Figure 4.** Overview of dobutamine-CMR images during diastole (A) and systole (B). x-Axis, dobutamine levels: 0 (baseline), 10, 20, and 30 μg dobutamine; y-axis, short-axis planes of grid-tagged images (basal and midventricular plane) and nontagged images (basal, midventricular, and apical plane). At 20 and 30 μg dobutamine, there is matching ischemia between nontagged and tagged images (arrows) of the inferior and septal wall on the basal and midventricular short-axis planes of the left ventricle.
Although they can be regarded as a "learning error," both patients were counted as having false-positive results.

The WMSI of the patients with a positive dobutamine-CMR study were mainly determined by WMAs in the basal and midventricular planes. Isolated apical WMAs were not encountered. If the apical plane was excluded from the analyses, the number of positive dobutamine-CMR studies would drop by 3%.

Target Heart Rate Rule
In many cardiac stress studies with echocardiography, atropine is given to increase heart rate in patients who fail to reach the target rate. In our study, no atropine was given, and the target-rate rule (target rate 85% of maximum; men 220 minus age/women 200 minus age) was not applied. It is known that the addition of atropine can enhance sensitivity to detect CAD. However, the target-rate rule, which forms the basis of applying this drug, has been questioned. The peak rate-pressure product in our study was similar to that reported by Nagel et al. Only peak heart rate was higher in their study, most likely because of the atropine. However, the mean diastolic and systolic blood pressure at rest and peak stress and the heart rate at rest were higher in our series. Maybe this was due to the fact that all antianginal medication was stopped over a longer period of time. Because of the side effects of atropine, patients are unable to drive a car after the study. To obviate the need for atropine and to obtain an adequate response to dobutamine, we prolonged infusion time of each dose from 3 to 6 minutes.

Myocardial Tagging
SPAMM is the most frequently used tagging sequence for CMR, which generates two orthogonal sets of parallel planes of magnetic saturation (grid-tagging) by a sequence of non-selective radiofrequency pulses. In the present study, grid-tagging was used at the basal and midventricular short-axis images only, because the tags were too broad in relation to the small apex of the left ventricle, giving rise to blurring and unacceptable image quality.

Other forms of tagging can give narrower tags, such as the DANTE-tagging sequence. In addition, an image-processing technique such as HARP (harmonic-phase) does not rely on the tags facing the same direction. These techniques were not available on our MR system. The quantitative HARP image processing method is based on the use of isolated spectral peaks in SPAMM-tagged MR images. Until now, quantitative assessment of myocardial strains in a single slice will take about 3 minutes, and analysis of a complete data set about 60 minutes. In our opinion, these quantitative image-processing times are still too long to perform a safe high-dose dobutamine-CMR study. Second, the additional value of quantitative analysis in the diagnosis of myocardial ischemia is probably limited, because the semiquantitative methods, including our method, has shown excellent results.

Recently, online analysis of WMA of the left ventricle was performed successfully with real-time CMR. In the future, real-time imaging may be an important additional tool to the standard breath-hold technique, perhaps in combination with quantitative analysis as well.

Complications
The major reasons for study failure were minor complications (n = 7) and inability to sustain breath-hold (n = 5), which is comparable to other studies.

One patient (0.5%) had ventricular fibrillation at the end of the study after 40 μg of dobutamine. After review of the images it was obvious that NWMA were already present at 20 μg, which was not noted during the study. This patient was ischemic at a level of 20 μg, and we overstressed the patient over 2 levels of dobutamine.

In a previous study, severe complications occurred in 0.25% of the patients, including ventricular fibrillation (0.07%) and sustained ventricular tachycardia (0.1%).

Follow-Up
We demonstrate that patients with a normal dobutamine-CMR study without baseline WMA had a MACE rate of 1.8% during the mean follow-up of 17.3 months. In a series of patients with a normal DSE, the annual MACE rate was 1.2% over a 5-year period. These results seem to be comparable; however, long-term follow-up studies are needed to determine the negative predictive value of dobutamine-CMR.

In the group of patients with a normal dobutamine-CMR study and baseline WMA, 4 of 14 (29%) patients showed a MACE within a mean follow-up of 17.3 months. The value of this complication rate, however, is uncertain because the number of patients in this group was limited. It is known that the presence of baseline WMA is a risk factor for the development of MACE. This group of patients with baseline WMA should be monitored closely during follow-up.

Study Limitations
First, because CAG was not performed in the patients with a negative dobutamine-CMR study, our data could be influenced by referral bias. The outcome of the dobutamine-CMR in this study was used as a direct arbiter for subsequent clinical follow-up. Initially, the additional values of the tagging data were unknown; however, the possibility of any adverse clinical effect of this strategy was regarded as minimal, since tagging was performed as an additional imaging test besides the standard nontagging images. The sensitivity and specificity of the test could not be determined directly, since not all patients were studied by CAG.

Second, images were analyzed semiquantitatively. Possible improvements could be acquired by using quantitative wall motion analysis; however, until now, it is a time-consuming procedure, and no decisions can be made during the study. We believe that it is crucial to stop a dobutamine-CMR study immediately when a patient becomes ischemic, since over-stressing can lead to ventricular fibrillation. A quantitative analysis has clinical potential when the results are available within a few seconds after each cine-acquisition.

Third, we used a 1-T MR system. The more standard 1.5-T systems can reduce cine-acquisition substantially, which improves patient acceptance and image quality. Also, the
entire procedure time can be shortened if 3-minute infusion time is used, as is a standard protocol in many centers.

Fourth, we used only 3 short-axis planes, whereas the apical short-axis was performed without tagging. This could produce sampling errors so that small areas of WMA may have been missed, especially in the apical plane.

Conclusions
In conclusion, we demonstrate that high-dose dobutamine-CMR with myocardial tagging improves the detection of NWMAs, which are indicative of myocardial ischemia. Dobutamine-CMR with tagging is not only a reliable but also a safe diagnostic technique in the analysis of myocardial ischemia. It reliably separates patients with a normal life expectancy from those at increased risk of major adverse cardiac events.

Acknowledgments
We thank Bernadette Blom, Wouter Stam, Marielle Broeders, and Truus den Besten for assistance in performing the CMR studies. The authors thank Dr J.C. de Groot for assistance in preparing the manuscript.

References
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Circulation. 2003;107:1592-1597; originally published online March 17, 2003;
doi: 10.1161/01.CIR.0000060544.41744.7C
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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