Reperfusion Injury on Magnetic Resonance Imaging After Carotid Revascularization

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Background and Purpose—Reperfusion injury can be revealed as delayed gadolinium enhancement in the subarachnoid space on a fluid-attenuated inversion recovery image, which is designated as a hyperintense acute reperfusion marker (HARM). We sought to investigate the occurrence and predictors of HARM and its association with new ischemic infarcts after carotid revascularization.

Methods—Forty-five patients who underwent carotid endarterectomy or stenting were prospectively enrolled. Diffusion-weighted imaging and fluid-attenuated inversion recovery were performed before and 24 hours after the procedures. Postprocedural fluid-attenuated inversion recovery was done after intravenous gadolinium injection.

Results—HARM was observed in 8 (17.8%) patients. Of these, 4 patients showed neurological deterioration associated with HARM. These symptomatic HARMs disappeared on follow-up magnetic resonance imaging. Patients with symptomatic HARM were older ($P=0.010$) and had more frequent leukoaraiosis ($P=0.012$) and higher postprocedural systolic blood pressure ($P=0.025$) than those without. New brain infarcts on postprocedural diffusion-weighted imaging were identified in 13 (28.9%) patients. HARM was not associated with new infarcts.

Conclusions—HARM after carotid revascularization is not uncommon. Symptomatic HARM was associated with old age, underlying leukoaraiosis, and postprocedural high blood pressure. (Stroke. 2014;45:602-604.)

Key Words: cerebral revascularization • reperfusion injury

Carotid revascularization procedures may be complicated by new brain infarcts, hyperperfusion syndrome, or reperfusion injury.1,2 Blood–brain barrier disruption in acute brain ischemia can be revealed as delayed gadolinium enhancement of the cerebrospinal fluid space on a fluid-attenuated inversion recovery (FLAIR) image, designated as a hyperintense acute reperfusion marker (HARM). HARM is reported to be associated with reperfusion injury, hemorrhagic transformation, and poor clinical outcome.3 HARM has been observed in patients with acute ischemic stroke with or without thrombolysis.3,4 However, incidence, associated factors, and the natural course of HARM after carotid revascularization have not yet been investigated. Whether HARM is associated with new ischemic infarcts is not clear either.

Methods
This study prospectively included patients who underwent carotid endarterectomy (CEA) or carotid artery stenting because of severe (≥70%) carotid stenosis. Patients who underwent emergency procedures, had contraindication to magnetic resonance imaging (MRI), and refused to consent were excluded. This study was approved by an institutional review board of Asan Medical Center, and written informed consent was obtained from each patient or legal guardian.

Patients received a 1.5-T MRI scan that included diffusion-weighted imaging (DWI) and FLAIR before and 24 hours after the procedures. DWI parameters included a repetition time/an echo time of 7500/84 ms, a matrix number of 128×128, and 2 b values of 0 and 1000 s/mm². The FLAIR image was obtained using a fast-spin echo sequence having repetition time/echo time of 10002/97.5 ms, an inversion time of 2200 ms, and a 256×128 matrix. For the detection of HARM, gadolinium was injected immediately after the procedures. Postprocedural fluid-attenuated inversion recovery was done after intravenous gadolinium injection.

The presence of HARM was reviewed by an experienced neurorlogist (A.-H.C.) blinded to the clinical information. The presence of ischemic lesions on DWI, leukoaraiosis, the degree of carotid stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria,1 and plaque nature were analyzed. Leukoaraiosis was regarded as present when mild or more severe periventricular and deep white matter hyperintensities were observed based on the Fazekas grading system.6 Clinical variables including demographics, risk factors, blood pressures, and type of procedures were collected. Systolic and diastolic blood pressures were obtained before, during, and after the procedures. The Mann–Whitney U test, Student t test, and Fisher exact test were used where appropriate. Multivariate analysis was not performed because of low event rates.

Received October 7, 2013; accepted November 8, 2013.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.003792/-/DC1.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.113.003792
Between July 2007 and December 2009, a total of 46 patients were enrolled. Excluding 1 patient who could not undergo postprocedural FLAIR, 45 patients were included for the final analysis. Of these, 4 cases had been previously reported as a case report. Thirty-five (77.8%) patients were male. The mean age was 67.7 (±10.0) years. CEA was performed in 29 patients. The degree of carotid stenosis was 83.5% (±8.6%).

On preprocedural FLAIR, HARM was not observed in any patients. After carotid revascularization, HARM was observed in 8 (17.8%) patients (Figures 1 and 2). In 4 (50%) patients, new neurological symptoms and signs related to HARM were observed (Figure 1). All 4 patients with symptomatic HARM showed a steady clinical improvement during the following days after strict blood pressure control. Symptomatic HARM disappeared on follow-up MRIs.

Patients with HARM were older than those without (74.1±5.3 versus 66.3±10.3 years; P=0.02; Table I in the online-only Data Supplement). The type of procedures was not associated with HARM (3/29 in CEA versus 5/16 in carotid artery stenting). Patients with symptomatic HARM were older (77.3±4.6 versus 66.7±10.0 years; P=0.010) and had more frequent leukoaraiosis (4/4 versus 12/41; P=0.012) and higher postprocedural systolic blood pressure (156.5±7.7 versus 137.3±22.2 mm Hg; P=0.025) than those without.

New infarcts on postprocedural DWI were identified in 13 (28.9%) patients (8/29 [27.6%] in CEA versus 5/16 [31.3%] in carotid artery stenting). Only 2 patients (2/13; 15.4%) showed a neurological deterioration related to new infarcts. HARM was not associated with the presence of new infarcts (P=0.20). Of 8 patients with HARM, 4 patients showed new coexisting infarcts. In these 4 patients, new postprocedural ischemic lesions were mostly located in the area of HARM.

**Discussion**

In this study, HARM was observed in 18% of patients undergoing carotid revascularization. Half of these patients developed new neurological symptoms related to HARM. This is consistent with a previous study that showed that HARM was associated with poor clinical outcome after acute ischemic stroke. It is interesting to note that symptomatic HARM (50%) was more frequent than new symptomatic DWI lesions (15%) in this study. We think that HARM could be considered a major cause of neurological complications after carotid revascularization.

Up until now, the incidence of HARM has been investigated only in patients with ischemic stroke (33%). The reason for the lower incidence in this study may lie in the difference in stroke stage (subacute/chronic versus acute), intervention or natural course, and sample size. The difference in the interval from the time of stroke onset or the procedure to the time of imaging may be another important factor: the median time from stroke onset to HARM observation in the previous study was 10 hours, whereas in this study, the time from the procedure to the MRI was 24 hours.

Old age, leukoaraiosis, and postprocedural high systolic blood pressure were all associated with the development of HARM.

**Figure 1.** Symptomatic hyperintense acute reperfusion marker (HARM). Postprocedural diffusion-weighted imaging (left of each panel) and fluid-attenuated inversion recovery (right) show new ischemic infarcts (A, B, D) and HARM (A–D). CEA indicates carotid endarterectomy.

**Figure 2.** Asymptomatic hyperintense acute reperfusion marker (HARM). Postprocedural diffusion-weighted imaging (left of each panel) and fluid-attenuated inversion recovery (right) show new ischemic infarcts (D) and HARM (A–D). CEA indicates carotid endarterectomy.
In aged brains, the degree of blood–brain barrier disruption to injury is greater than in younger brains, resulting in decreased repair responses. Regarding leukoaraiosis, blood–brain barrier disruption and vasogenic edema would be attributable to the pathogenesis of leukoaraiosis. Age is the most important risk factor for leukoaraiosis. Thus, it is plausible that age and leukoaraiosis, both of which are related to a vulnerable blood–brain barrier, might be predictors for HARM after revascularization. The relationship between postprocedural high blood pressure and the development of HARM in this study is in line with the previous notion that postoperative hypertension is a risk for cerebral hyperperfusion syndrome after CEA. Considering this observation, strict blood pressure control should be encouraged after cerebral revascularization for the prevention of HARM.

The occurrence of HARM and the occurrence of new brain infarcts after procedures were not significantly associated; it seems that they are distinct pathological phenomena. However, in 4 patients who had both HARM and new DWI lesions, new infarcts were located mostly in the HARM area. This is likely to be because embolic infarcts preferentially occur in reperfused areas, where HARM develops.

Several limitations should be noted. Despite the prospective nature of this study, the sample size was small. CEA and carotid artery stenting were lumped in the analysis, although procedure types were not associated with HARM. In patients with asymptomatic HARM, follow-up MRI was not planned. However, because even symptomatic HARM (the more severe form) disappeared on follow-up, we assume that asymptomatic HARM might be reversible.

Sources of Funding
This study was supported by grants from the National Research Foundation of Korea (NRF) funded by the Korea government (MEST, No. 2011-0016868) and the Korea Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A121996).

Disclosures
None.

References
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Stroke. 2014;45:602-604; originally published online December 17, 2013;
doi: 10.1161/STROKEAHA.113.003792

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### Supplemental Table I. Characteristics between patients with and without HARM

<table>
<thead>
<tr>
<th></th>
<th>All HARMs</th>
<th></th>
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<th>Symptomatic HARM</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=8)</td>
<td>No (n=37)</td>
<td>p</td>
<td>Yes (n=4)</td>
<td>No (n=41)</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>74.1±5.3</td>
<td>66.3±10.3</td>
<td>0.020</td>
<td>77.3±4.6</td>
<td>66.7±10.0</td>
<td>0.010</td>
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<tr>
<td>Sex, male</td>
<td>6 (75.0%)</td>
<td>29 (78.4%)</td>
<td>&gt;0.999</td>
<td>4 (100.0%)</td>
<td>31 (75.6%)</td>
<td>0.561</td>
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<tr>
<td>Hypertension</td>
<td>6 (75.0%)</td>
<td>32 (86.5%)</td>
<td>0.590</td>
<td>3 (75.0%)</td>
<td>35 (85.4%)</td>
<td>0.505</td>
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<td>Diabetes</td>
<td>2 (25.0%)</td>
<td>10 (27.0%)</td>
<td>&gt;0.999</td>
<td>1 (25.0%)</td>
<td>11 (26.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (25.0%)</td>
<td>5 (13.5%)</td>
<td>0.590</td>
<td>1 (25.0%)</td>
<td>6 (14.6%)</td>
<td>0.505</td>
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<tr>
<td>Smoking</td>
<td>2 (25.0%)</td>
<td>15 (40.5%)</td>
<td>0.690</td>
<td>1 (25.0%)</td>
<td>16 (39.0%)</td>
<td>&gt;0.999</td>
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<tr>
<td>Preprocedure SBP (mmHg)</td>
<td>158.1±21.3</td>
<td>160.9±24.0</td>
<td>0.788</td>
<td>158.0±22.4</td>
<td>160.6±23.6</td>
<td>0.870</td>
</tr>
<tr>
<td>Postprocedure SBP (mmHg)</td>
<td>138.0±25.0</td>
<td>139.3±21.7</td>
<td>0.787</td>
<td>156.5±7.7</td>
<td>137.3±22.2</td>
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<tr>
<td>Carotid stenosis, %</td>
<td>79.9±7.1</td>
<td>83.1±1.5</td>
<td>0.342</td>
<td>84.8±6.1</td>
<td>82.3±8.8</td>
<td>0.622</td>
</tr>
<tr>
<td>Echolucent plaque (n=30)</td>
<td>3 (37.5%)</td>
<td>11 (29.7%)</td>
<td>&gt;0.999</td>
<td>1 (25.0%)</td>
<td>13 (31.7%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>4 (50.0%)</td>
<td>12 (32.4%)</td>
<td>0.427</td>
<td>4 (100.0%)</td>
<td>12 (29.3%)</td>
<td>0.012</td>
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<tr>
<td>CEA</td>
<td>3 (37.5%)</td>
<td>26 (70.3%)</td>
<td>0.111</td>
<td>1 (25.0%)</td>
<td>28 (68.3%)</td>
<td>0.121</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD or number (column %).

HARM, hyperintense acute reperfusion marker; CEA, carotid endarterectomy; SBP, systolic blood pressure

* All HARMs include symptomatic and asymptomatic HARM.