Association of Intraplaque Hemorrhage and Acute Infarction in Patients With Basilar Artery Plaque

Jin Hee Yu, MD; Hyo Sung Kwak, MD, PhD; Gyung Ho Chung, MD, PhD; Seung Bae Hwang, MD; Mi Sung Park, MD, PhD; Seong Hoon Park, MD, PhD

Background and Purpose—High-resolution magnetic resonance imaging (HRMRI) is ideal for serial examination of diseased arterial walls because it is noninvasive and has superior capability of discriminating tissue characteristics. The aim of this study is to evaluate the prevalence and clinical relevance of intraplaque hemorrhage (IPH) in patients with basilar artery (BA) atherosclerosis using HRMRI.

Methods—We analyzed HRMRI and clinical data from 74 patients (45 symptomatic and 29 asymptomatic), all of whom had >50% BA stenosis. High-signal intensity within a BA plaque on magnetization-prepared rapid acquisition with gradient-echo was defined as an area with an intensity that was >150% of the signal from the adjacent muscle. The relationship between IPH within a BA plaque region and clinical presentation was analyzed.

Results—Thirty patients were positive for IPH on HRMRI (42.3%, 24 symptomatic and 6 asymptomatic). Symptomatic lesions in the MR-positive IPH group were significantly more prevalent than in the MR-negative group (80.0% versus 48.8%; P<0.01). Also, MR-predicted IPH was significantly more prevalent in the high-grade stenosis group (P<0.001) than in the low-grade group. The relative risk of an acute focal stroke event among patients who were magnetization-prepared rapid acquisition with gradient-echo–positive for IPH compared with patients who were magnetization-prepared rapid acquisition with gradient-echo–negative was 1.64.

Conclusions—IPH within a BA plaque region on HRMRI is highly prevalent and is associated with acute stroke.

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Key Words: atherosclerosis ■ basilar artery ■ magnetic resonance imaging ■ risk factors ■ stroke

Atherosclerosis is a disease in which plaque builds up inside the arteries. As the plaques harden, the arteries narrow, which can lead to serious problems including heart attack, stroke, or even death. Intraplaque hemorrhage (IPH) is commonly observed in atherosclerotic plaques and is thought to be caused by a rupture in the plaque neovascularure. These microvessels are fragile because they are not supported by smooth muscle cells, and there is focal discontinuity in the endothelial lining. Neovessel density is positively correlated with necrotic core formation and inflammatory infiltrates. Therefore, the presence of intraplaque extravasation and bleeding is regarded as a feature that contributes to local lipid deposition and acts as a proinflammatory source. IPH in carotid atherosclerotic plaques is significantly associated with more rapid progression of plaque size, the presence of a lipid-rich necrotic core, and the progression of luminal stenosis.

High-resolution magnetic resonance imaging (HRMRI) is ideal for serial examinations of diseased arterial walls because it is noninvasive and has superior capability of discriminating tissue characteristics when compared with other imaging modalities. T1-weighted MR sequences and 3-dimensional (3D) time-of-flight (TOF) magnetic resonance angiography (MRA) are commonly used to detect IPH. Far more accurate detection of IPH is now accomplished using advanced heavily T1-weighted techniques including magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequencing and simultaneous noncontrast. MPRAGE sequences for the detection of IPH using histological confirmation have significantly higher sensitivity and specificity than conventional T1 or TOF-MRI. However, relevant studies, although also concerned with IPH and its association with imaging findings and clinical symptoms, have mostly focused on disease in the carotid artery.

Recently, Xu et al reported that high-signal intensity from T1-weighted imaging of the plaques in the middle cerebral artery (MCA) was associated with risk of ipsilateral stroke using HRMRI. However, they did not use a new sequence for the detection of IPH, and no previous study has evaluated the presence of IPH in basilar artery (BA) plaques with HRMRI.
In this study, we evaluated the prevalence and clinical relevance of IPH in patients with BA plaque using HRMRI.

Materials and Methods

Patients

This study was approved by the local institutional review board, and informed consent was obtained from all patients before imaging. Between September 2011 and August 2014, we consecutively selected patients for BA stenosis using TOF-MRA. During this period, all patients underwent standard brain MRI/MRA to detect any neurological symptoms or signs, such as headache, dizziness, giddiness or vertigo, or stroke, and MR protocols to evaluate the acute stroke, and patient BA stenosis status was documented. We performed the HRMRI for evaluation of plaque in patients with BA stenosis within 2 weeks after initial MR examination. Symptomatic patients were eligible for enrollment if we found evidence of an ischemic stroke or transient ischemic attack within the stenotic area of the BA and a hyperintense signal on diffusion-weighted imaging with an associated decreased signal on the apparent diffusion coefficient map within the preceding week. Patients with any of the following features were excluded from the analysis: (1) coexistent unilateral or bilateral vertebral artery stenosis or luminal irregularity >50% on MRA or HRMRI; (2) <50% BA stenosis on MRA and HRMRI; or (3) nonatherosclerotic vasculopathy, such as dissection or Moyamoya disease. BA dissection was defined as a wall thickening with low-signal intensity because of intimal flap-on black-blood T2-weighted imaging and high-signal intensity because of intimal flap-on TOF-MRA.13

During the study period, 91 patients underwent HRMRI. Seventeen patients were excluded, including 4 patients with <50% BA stenosis on axial images of HRMRI, 9 patients with coexistent unilateral or bilateral vertebral artery stenosis or luminal irregularity >50%, and 4 patients with BA dissection. Seventy-four patients were included in this study.

MRI Protocol

MRI was performed with a 3 T MR scanner (Achieva; Philips Medical Systems, Amsterdam, Netherlands) with a 16-channel head coil. All patients initially underwent conventional brain MRI, which included 3D TOF-MRA. TOF-MRA of the axial plane was obtained for each patient, and data were reconstructed using a dedicated online postprocessing tool to determine blood vessel architecture.

The HRMRI protocol included 4 different scans: T1-weighted, T2-weighted, TOF, and MPRAGE. T1-weighted imaging was acquired using a 2D turbo spin-echo sequence with the following imaging parameters: repetition time/echo time=800/10 ms, field of view=140x140 mm, matrix size=140x150, slice thickness=2.0 mm, echo train length=10, and number of excitations=2. For T2-weighted HRMRI scans, the turbo spin-echo sequence used a repetition time/echo time=3100/80 ms, field of view=140x140 mm, matrix size=140x140, slice thickness=3.0 mm, echo train length=50, and number of excitations=2. The imaging parameters for the TOF-MRA scan were as follows: repetition time/echo time=18/3.8 ms, flip angle=16°, field of view=140x140 mm, matrix size=312x165, slice thickness=1.0 mm, echo train length=1, and number of excitations=3. For 3D MPRAGE sequencing, segmental acquisition was performed using sequence repetition time, inversion preparation time, and the phase encoding order from the MPRAGE sequences, adjusted to optimally identify IPH as hyperintense. Image parameters were as follows: repetition time/echo time/inversion time=8.8/5.3/304 ms, flip angle=15°, echo train length=52, field of view=140x140 mm, matrix size=216x198. The black-blood technique with preregional 80-mm-thick saturation pulses to saturate incoming arterial flow was used for all scans. The longitudinal coverage of each artery was 22 to 24 mm. The scan time was 3 to 4 minutes for each scan. The total scan time was ≈25 to 30 minutes, and patients remained in the MR machine for ≈35 to 45 minutes.

MRI Analysis

We searched for the presence of BA plaques among all samples using HRMRI. Two neuroradiologists performed all of these procedures. Plaque was defined as a thickening of the focal wall relative to image slices from beneath or above the focal wall, as identified on T2- and T1-weighted imaging. BA plaques were considered to be IPH-positive on MPRAGE when high-signal intensity was detected within the plaques. High-signal intensity was defined as an area with >150% intensity of the signal of the adjacent muscle.

The relationship between BA plaque IPH and clinical presentation was analyzed. All slices of the 4 sequences of a BA plaque on HRMRI were reviewed by 2 experienced image readers who were blinded to the clinical details and the diffusion-weighted images. Consensus interpretation was used for the final analysis when the image readers’ interpretations differed.

A positive diffusion-weighted imaging (DWI) signal was defined as a hyperintense signal on DWI trace with an associated decreased signal on the apparent diffusion coefficient map, corresponding to an acute ischemic event at the time of the scan. Acute territorial ischemic events were first classified based on distribution (ipsilateral internal carotid artery territory, ipsilateral basal ganglia, or posterior circulation), and then only DWI-positive events in the posterior circulation were considered DWI positive. DWI images were interpreted by an experienced neuroradiologist who was blinded to the carotid MPRAGE results.

Statistical Analysis

Continuous values are expressed as medians or ranges and categorical data as counts and percentages. Continuous and categorical variables were compared among these groups using the Mann–Whitney U test and Fisher exact test, respectively. Likelihood ratios from a 2x2 table were used to estimate the relative risk of a cerebrovascular ischemic event in MR-positive IPH patients with a 95% confidence interval. Statistical significance was defined as P<0.05. All statistical analyses were performed using R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Seventy-three patients (median age, 72.5 years; range, 57–83 years) with >50% BA stenosis on axial HRMRI images and plaque qualified for study inclusion. Of these patients, 45 were symptomatic and 29 were asymptomatic. The clinical characteristics and imaging findings of the MR-positive and MR-negative IPH groups are shown in Table 1. Thirty patients (41.1%) had MR-positive IPH within their BA plaques. Symptomatic lesions were significantly more common in the MR-positive IPH group than in the MR-negative IPH group.

Table 1. Clinical Characteristics and Imaging Findings of the MR-Positive and MR-Negative Intraplaque Hemorrhage Groups

<table>
<thead>
<tr>
<th></th>
<th>MR Positive (n=30)</th>
<th>MR Negative (n=43)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>75</td>
<td>71</td>
<td>ns</td>
</tr>
<tr>
<td>Age range, y</td>
<td>65–82</td>
<td>57–83</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>14 (46.7%)</td>
<td>27 (62.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (26.7%)</td>
<td>12 (27.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (43.3%)</td>
<td>21 (48.8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Current smoking</td>
<td>6 (20.0%)</td>
<td>11 (25.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (33.3%)</td>
<td>15 (34.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Previous heart disease</td>
<td>4 (13.3%)</td>
<td>8 (18.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>24 (80.0%)</td>
<td>21 (48.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>72.9±8.7</td>
<td>62.2±13.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MR indicates magnetic resonance.
in symptomatic patients was significantly higher in prevalence when compared with asymptomatic patients.

Previous studies reported an association between BA plaque and symptoms on HRMRI. In these studies, BA atherosclerotic plaques were mainly distributed at the ventral site of the artery. Among patients with small medial pontine lesions, 73% had BA plaques that were detected by HRMRI. This finding suggests that medial pontine lesions are because of penetrating artery disease secondary to BA atherosclerosis. However, to our knowledge, no previous study has evaluated the presence of IPH in BA plaques using HRMRI. Xu et al reported that high-signal intensity on T1 was identified on HRMRI in 10.1% of MCA stenosis cases, and 19.6% of symptomatic and 3.2% of asymptomatic MCA stenosis cases. However, this study used only T1-weighted fat-suppressed imaging.

Early identification of IPH is important for decreasing the risk of future sequelae and optimizing treatment plans. IPH presence promotes immediate and long-term plaque progression, and IPH seems to alter the biology and natural history of carotid atherosclerosis. T1-weighted MR sequences are commonly used to detect IPH because the degradation of a hemorrhage produces methemoglobin, which results in T1 shortening and correspondingly causes high-signal intensity on T1-weighted MRI. Among the T1-weighted MR sequences, black-blood T1-weighted fast spin-echo and 3D TOF angiography are currently used for clinical examination. In the present study, we used MPRAGE because recent research has shown that this sequence has higher sensitivity and specificity in detecting hemorrhage compared with black-blood T1-weighted fast spin-echo and TOF angiography. The MPRAGE sequence combined with contrast-enhanced T1-weighted and TOF angiography is more practical for the evaluation of carotid plaque components, including IPH. In this study, the heavily T1-weighted signal of the MPRAGE sequence was accomplished by a magnetization-prepared inversion pulse. On the basis of signal simulation that incorporated T1 values of muscle, blood, and hemorrhage, we selected the segment repetition time and T1 in the MPRAGE sequence to suppress the flowing blood signal and enhance tissues with short T1 relative to muscle.

**Discussion**

Previous studies found that high-signal intensity on T1-weighted imaging with HRMRI is highly suggestive of IPH presence and is associated with symptomatic atherosclerotic plaque and rapid plaque progression. Xu et al reported that the occurrence rate of high-intensity signal was significantly different between symptomatic and asymptomatic MCAs. In our study, MR-positive IPHs within BA plaques were found in 30 patients (42.3%). MR-positive IPH

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**Table 2. MPRAGE-Positive Intraplaque Hemorrhage in Patients With Basilar Artery Plaques**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=73)</th>
<th>MPRAGE Positive (n=30)</th>
<th>MPRAGE Negative (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic (n=45)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevalence of MPRAGE (+), %</td>
<td>41.1</td>
<td></td>
<td></td>
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<tr>
<td>Specificity, %</td>
<td>46.5 (32.6–60.5)</td>
<td></td>
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<tr>
<td>Sensitivity, %</td>
<td>80.0 (66.7–93.3)</td>
<td></td>
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<tr>
<td>Accuracy, %</td>
<td>53.3 (37.8–68.9)</td>
<td></td>
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<tr>
<td>Relative risk</td>
<td>1.64 (1.15–2.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P value (2-tailed)</strong></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specificity, sensitivity, and accuracy values are reported with exact binomial 95% CIs. Specificity, sensitivity, and accuracy refer to stroke risk in patients with MPRAGE-positive intraplaque hemorrhage into the basilar artery plaque. Relative risk values are reported with 95% CI. CI indicates confidence interval; and MPRAGE, magnetization-prepared rapid acquisition with gradient-echo.

(80.0% versus 48.8%; P<0.01). MR-predicted IPH was significantly more prevalent in the high-grade stenosis group than in the low-grade group (P<0.001).

Data from patients who have MPRAGE-positive IPH and symptomatic lesions with BA plaques are shown in Table 2. Patients who had MPRAGE-positive IPH within their BA plaque were associated with increased risk of an acute focal stroke event (P<0.01; Figures 1 and 2). The relative risk of an acute focal stroke event with an MPRAGE-positive IPH in patients with BA plaques compared with MPRAGE-negative patients was 1.64.

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**Figure 1.** A 72-year-old woman with basilar artery plaque and acute pontine infarction. **A,** Diffusion-weighted imaging shows diffusion restriction in the left pons. **B,** Black-blood T2-weighted imaging shows eccentric plaque in the ventral portion of the basilar artery (arrows). **C,** T1-weighted imaging shows high-signal intensity, indicating plaque in the basilar artery (arrows). **D,** Magnetization-prepared rapid acquisition with gradient-echo imaging shows bright and high-signal intensity in the basilar artery plaque (arrows). This finding suggests that there is an intraplaque hemorrhage in the basilar artery.
In the present study, MR-positive IPHs were observed on HRMRI in 42.3% of plaques. MR-positive IPHs were observed on HRMRI in 54.5% of symptomatic and in 20.0% of asymptomatic plaques. The prevalence of MR-positive IPH was higher in our study than results from a previous study of MCA plaques (42.3% versus 10.1%). The prevalence of MP-positive IPH in symptomatic BA plaque patients was also higher than that among MCA plaque patients (54.5% versus 19.6%). These findings suggest that the BA, compared with the MCA, has a larger wall area and can be seen better with axial imaging. In addition, the BA has more eustemal space when compared with the MCA. Therefore, BA plaque can be visualized more accurately on HRMRI than plaque in the MCA. We used multicontrast imaging, such as T1-weighted, TOF-MRA, and MPRAGE sequences, for evaluation of IPH. In our study, the stenotic degree of BA plaques in the IPH group was significantly higher than in the non-IPH group. This finding was similar to that of previous carotid plaque studies.14,15

Our study has several limitations. First, we lack a gold standard histological reference. Ota et al. evaluated the diagnostic performance of 3 T1-weighted 3.0 T MR sequences using carotid IPH imaging with histological analysis as the reference standard. MPRAGE sequence, when compared with T1-weighted fast spin-echo and TOF sequences, demonstrated higher diagnostic capability for the detection and quantification of IPH. Therefore, we concluded that carotid MPRAGE-positive images strongly suggested the presence of IPH. Second, our study focused on atherosclerotic lesions in the BA, and patients with vertebral artery plaques were excluded from this study. Common causes of acute ischemic stroke are major arterial atheroma, cardioembolic sources, microvascular disease, and cryptogenic factors. Acute ischemic stroke within vulnerable carotid plaques, such as IPHs, fibrous cap ruptures, or ulcers, was relatively low in prevalence when compared with other cardiac sources. Finally, MPRAGE images have lower accuracy and are more poorly correlated with histology in patients with small IPH and calcified lesions. We did not analyze small IPH combined calcification in BA plaque because calcification of the BA and MCA is less prevalent than that of the vertebral artery and internal carotid artery.19

Conclusions
IPH within a BA plaque, as detected on HRMRI, was highly prevalent. Furthermore, MR-positive IPHs in patients with BA plaques were associated with higher risk of acute ischemic stroke.

Disclosures
None.

References


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