Contrast enhanced magnetic resonance angiography has low sensitivity for evaluating stenosis in the Lt. vertebral artery

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Background

Contrast enhanced magnetic resonance angiography (CE-MRA) has been reported to have high sensitivity and specificity for detecting ≥50% stenosis of vertebral arteries. However, previous studies used intra-arterial digital subtraction catheter angiography (IAA) as the gold standard, and may therefore have missed atheroma with positive remodeling. We reevaluated the sensitivity and specificity of CE-MRA for detecting stenosis of intracranial vertebral arteries (V4 segment) in the presence of positive remodeling.

Methods

Ninety-seven patients with posterior circulation stroke who underwent CE-MRA were reviewed retrospectively by two neuroradiologists. Diagnostic accuracy of CE-MRA for evaluating stenosis of intracranial vertebral artery was calculated. The gold standard was a consensus reading by two different experienced neuroradiologists of combination of CE-MRA images, high-resolution axial images, and curved multiplanar images.

Results

Both readers detected ≥50% stenosis in the Rt. vertebral artery with fair sensitivity and specificity (0.83/0.95 for reader 1 and 0.91/0.90 for reader 2). However, the sensitivity for detecting ≥50% stenosis in the Lt. vertebral artery was markedly lower for both readers (0.5/0.95 for reader 1 and 0.65/0.91 for reader 2).

Conclusions

Atheroma with positive remodeling increased the false negative rate of CE-MRA for detecting stenosis of intracranial vertebral arteries in posterior circulation stroke. Specifically, CE-MRA appears to have low sensitivity for detection of stenosis in the Lt. vertebral artery.

Key Words: Magnetic resonance angiography, vertebrobasilar disease, stenosis, atheroma, positive remodeling
**Background**

Twenty percent of strokes are posterior circulation strokes,[1, 2] and one quarter of patients with posterior circulation stroke are known to have vertebral artery stenosis that might be the cause of stroke due to an arterial embolism[3]. Considering the high rate of recurrence of posterior circulation stroke[4], vertebral artery stenosis should be diagnosed accurately and treated properly. Cerebral angiography is regarded as the gold standard for the evaluation of vertebral artery stenosis. However, it is invasive. Recently, CE-MRA has been reported to be a good alternative to cerebral angiography as it has been shown to have good sensitivity and specificity for evaluation of vertebral artery stenosis[5]. However, previous studies have regarded cerebral angiography as the gold standard, and did not consider extraluminal atheroma and positive remodeling effects. The aim of this study was to evaluate the false negative rate of contrast-enhanced MR angiography for intracranial vertebral artery stenosis in posterior circulation stroke.

**Methods**

**Patients**

The Institutional Review Board of Gangnam Severance Hospital deemed approval of this retrospective trial unnecessary. We searched our database for patients with newly developed acute infarction in the posterior circulation (cerebellum, midbrain, pons, and medulla) who underwent CE-MRA from January 2011 through June 2013. Multiple infarcts located in the posterior circulation as well as the anterior circulation were excluded as the embolic source for these events was more likely the heart or aortic arch than the vertebral artery. If the cardiogenic embolic source was found by cardiac work-up (Transthoracic Echocardiogram and 24 hour Holter ECG monitoring), the patient was excluded. If extracranial vertebral
artery stenosis was suspected, these cases were also excluded, because an additional proximal underlying stenosis may influence the results. Finally, a total of 97 patients were included (72 women, 25 men; mean age 64 years; age range, 34-92 years). Infarct territories comprised the cerebellum (n=36), midbrain (n=3), pons (n=44), and medulla (n=14).

**Image Acquisition**

Brain MR imaging was performed using 3T MR units (Discovery MR750; GE Healthcare, Milwaukee, WI) in all patients. T2 axial turbo spin echo images (TR/TE =5414/96 ms, thickness = 4 mm, field of view = 210x210 mm, matrix =352x352) and axial diffusion weighted images (TR/TE =8000/71.6 ms, thickness= 3 mm, field of view=230x230, matrix=160x160, flip angle =90, b=1000) were acquired. After injection of 0.1 mmol/kg gadobutrol, three dimensional Spoiled Gradient Echo (SPGR) sequences (TR /TE =8.29/3.28; thickness =1, field of view =220x220, matrix=256x256 [reconstructed to 512x512], flip angle=12, reconstructed voxel=0.430x0.430x1 mm) and MRA (TR/TE=4.7/1.6 ms, thickness =1.4 mm, field of view = 310x310 mm, matrix =416x320 [reconstructed to 512x512], flip angle =25) were performed sequentially.

**Image analysis**

Two readers independently evaluated the CE- MRA images. The first reader (XXX) is a resident with 2 years of experience in reading brain MRIs. The second reader is a board-certified radiologist (XXX) with 7 years of experience of reading brain MRIs. Both readers were blinded to patients’ clinical information. They were asked to identify stenosis in both intracranial vertebral arteries (V4 segment). If there were multiple stenoses in V4 segment, the study coordinator (xxx) recorded the most severe stenosis that was discovered by reader 1 at the time of the reading process. Reader 2 was then asked to evaluate the matching lesion on
same MRA scan after 2 weeks. Stenosis > 50% was noted, because this can cause stroke and is the cut-off value for further intervention[6]. Stenoses were graded based on the North American Symptomatic Carotid Endarterectomy Trial method[7], but simple visual inspection was used rather than measuring the diameter. A consensus reading by two senior radiologists (XXX and XXX with 17 and 27 years of experience in reading brain MRIs, respectively) served as the reference standard. To achieve the best possible diagnostic accuracy, these two radiologists used high resolution contrast-enhanced SPGR images, T2 axial images, contrast-enhanced MRA images, and high-resolution multiplanar reconstruction images as well as a follow-up examination. They used the diameter of the vessel (vessel lumen + atheroma) at the stenotic level rather than the proximal normal diameter as the reference diameter when they evaluated the grade of stenosis.

Statistical analysis
Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Interobserver agreement between the two primary readers was analyzed using kappa statistics. A kappa value of less than 0.20 indicates slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81 or greater, nearly perfect agreement. Sensitivity and specificity of CE-MRA for detection of stenosis of vertebral arteries were calculated.

Results
Of a total of 97 Rt. vertebral arteries, 46 vessels showed stenosis. Twenty-four of 46 showed ≥50% stenosis. Of a total of 97 Lt. vertebral arteries, 53 vessels showed stenosis, and 27 of these 53 showed ≥50% stenosis. Interobserver agreement between the inexperienced reader
and experienced reader in identifying stenosis and ≥50% stenosis is summarized in Table 1. There was excellent interobserver agreement (k value, 0.83) in identifying stenosis in the Rt. vertebral artery. Interobserver agreement for ≥50% stenosis was also good (k value, 0.79). Interobserver agreement for stenosis and ≥50% stenosis in the Lt. vertebral artery was good (k value; 0.74 and 0.70 respectively). Sensitivity and specificity of CE-MRA for detection of stenosis and ≥50% stenosis in both vertebral arteries are summarized in Table 2. Both the inexperienced and experienced neuroradiologist detected stenosis in the Rt. vertebral artery with fair sensitivity and specificity (0.78/0.86 and 0.86/0.86, respectively). For ≥50% stenosis in the Rt. vertebral artery similar levels of sensitivity and specificity were obtained (0.83/0.95 for the inexperienced reader and 0.91/0.90 for the experienced reader). However, sensitivities for the Lt. vertebral artery were low for both readers. The inexperienced reader had a sensitivity of 0.66 and a specificity of 0.89 for detecting stenosis of the Lt. vertebral artery, while the experienced reader had a sensitivity of 0.78 and a specificity of 0.93. For ≥50% stenosis, even lower levels of sensitivities were obtained (0.5 for the inexperienced reader and 0.65 for the experienced reader; the specificities were 0.95 and 0.91, respectively).

Discussion

Khan et al.[5] showed that contrast-enhanced MR angiography had high sensitivity and specificity for the detection of vertebral artery stenosis. However, they used intra-arterial digital subtraction catheter angiography (IAA) as the gold standard. IAA could miss positive remodeling in atherosclerosis because this may not decrease the diameter of the vessel lumen. Evaluation of positive remodeling is important because it is associated with a significantly higher prevalence of stroke than negative remodeling[8-11]. Therefore, we re-investigated the diagnostic accuracy of CE-MRA for the detection of stenosis in vertebral arteries. Although there were false negatives induced by positive remodeling when diagnosing ≥50%
stenosis in the Rt. vertebral artery (2 out of 4 for the inexperienced reader, 2 out of 2 for the experienced reader), levels of sensitivity (0.83 for reader 1 and 0.91 for reader 2) were similar to those obtained in previous studies that used IAA as the gold standard (0.93[79.8 to 99.3])[6]. Furthermore, interobserver agreement for ≥50% stenosis in the Rt. vertebral artery was close to excellent (k value, 0.79). However, for the Lt. vertebral artery, both inexperienced and experienced readers detected ≥50% stenosis with low sensitivity (0.5 for the inexperienced reader, 0.65 for the experienced reader). The inexperienced reader missed 13 vessels with ≥50% stenosis. Eight of a total of 13 (61%) vessels had atheroma and positive remodeling. Four of 13 (30%) cases were regarded as hypoplasia rather than true stenosis at the reading process. The inexperienced reader missed one vessel (9%) because the vertebral arteries were too small to identify ≥50% stenosis. The experienced reader missed nine vessels with ≥50% stenosis in the Lt. vertebral artery. Seven of these nine vessels (78%) showed positive remodeling. One of the nine (11%) cases was due to hypoplasia and another one of the nine (11%) cases had small vessels. Atheroma with positive remodeling in the Lt. vertebral artery was the main cause of the decrease in sensitivity of contrast-enhanced MRA for the detection of ≥50% stenosis, regardless of reading expertise. One notable finding is the difference in sensitivity of contrast-enhanced MRA for detecting stenosis in the Rt. vertebral artery versus the Lt. vertebral artery. Positive remodeling appears to underlie these differences in detection sensitivity. Very few studies have reported the incidence of positive remodeling in both vertebral arteries. However, several studies in the coronary artery reported arterial remodeling occur at specific segments of coronary artery[12, 13]. Positive remodeling appears to be associated with blood flow, shear stress force and inflammatory mechanism[14]. However, exact mechanism is still unknown. Our result that positive remodeling occurs more in the Lt. vertebral artery than the Rt. vertebral artery should be further investigated in future studies of a larger patient population.
The inexperienced reader missed 17 stenotic vessels in the Lt. vertebral artery. Thirteen of these 17 vessels (76%) showed ≥50% stenosis. The experienced reader missed 11 stenotic vessels in the Lt. vertebral artery. Nine of these 11 (81%) had ≥50% stenosis. In other words, CE-MRA appears more likely to miss cases with ≥50% stenosis than cases with < 50% stenosis, even though the former are more clinically important.

Other study had several limitations. Firstly, we did not include posterior cerebral artery (PCA) territory infarctions because our medical record system does not have the search word “PCA territory”. However, all other posterior circulation territories were included. Second, we focused only on intracranial vertebral arteries and did not examine extra-cranial vertebral arteries, because high resolution SPGR and axial T2WI do not cover the extra cranial vertebral arteries. However, intracranial vertebral arteries stenosis is associated with a greater incidence of posterior circulation TIA, stroke, and death than extracranial vertebral artery stenosis[15]. Third, the grade of stenosis was evaluated by visual inspection rather than direct measurement. However, the grade of stenosis was simply stratified into stenosis and ≥50% stenosis. Qualitative visual evaluation may not produce the significant error in this simple stratification. Forth, in our study, if there were multiple stenoses in one vertebral artery, only the most significant stenosis was included. Therefore, we were not able to precisely evaluate the diagnostic accuracy of contrast-enhanced MRA for mild stenosis. However, we argue that evaluation of ≥50% stenosis is more important from a clinical perspective because it is more commonly associated with stroke and is the cut-off value for further intervention. Lastly, there was no correlation to IAA, which might provide more interesting data of false negative rates of endoluminal imaging such as IAA and CE-MRA.
Conclusion

Atheroma with positive remodeling increased the false negative rate of CE-MRA for detecting stenosis of intracranial vertebral arteries in posterior circulation stroke. Specifically, CE-MRA appears to have low sensitivity for detection of stenosis in the Lt. vertebral artery. This issue can be addressed by examining high-resolution axial images and MPR images to detect atheroma with positive remodeling.

Abbreviations

CE-MRA: Contrast enhanced magnetic resonance angiography; SPGR: Spoiled Gradient Echo; IAA: intra-arterial digital subtraction catheter angiography

Competing interests

The authors declare that they have no competing interest.

Authors’ contribution

S.J.A did the literature research, interpreted data and drafted the manuscript. M.R.Y interpreted data and performed the statistical analysis. S.H.S revised manuscript critically. K.Y.L and S.K.L collected the data. T.S.C participated its design and coordination and revised the manuscript. All authors read and approved the final manuscript.

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References


Figure legends

Figure 1. A 71-year-old female with medulla infarction. Both readers missed the $\geq 50\%$ stenosis between the arrows in the Lt. vertebral artery (A). High-resolution contrast-enhanced SPGR (B) and the curved multiplanar image (C) showed long segmental atheroma with positive remodeling.

Figure 2. A 70-year-old female with cerebellar infarction. Both readers diagnosed hypoplasia in the Lt. distal vertebral artery (arrow) (A). Contrast enhanced SPGR demonstrated total occlusion of the Lt. distal vertebral artery.
Table 1. Interobserver agreement between the inexperienced and experienced neuroradiologists for identification of stenosis and ≥50% stenosis.

<table>
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<tr>
<th>Stenosis (kappa ± SD)</th>
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<td>Rt. vertebral artery</td>
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<td>Lt. vertebral artery</td>
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<td>0.79±0.07</td>
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<td>0.70±0.09</td>
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Table 2. Diagnostic accuracy of contrast-enhanced MRA for evaluation of vertebral arteries.

<table>
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<tr>
<th>Stenosis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>Inexperienced neuroradiologist</td>
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<td>0.86</td>
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<td>10</td>
<td>0.86</td>
<td>0.86</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Experienced neuroradiologist</td>
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<tr>
<td></td>
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<td>0.89</td>
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<td>≥50% stenosis</td>
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<td>0.65</td>
<td>0.91</td>
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<td>9</td>
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</table>

Note. RV= Rt. Vertebral artery, LV= Lt. vertebral artery.
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Figure 2. A 70-year-old female with cerebellar infarction. Both readers diagnosed hypoplasia in the Lt. distal vertebral artery (arrow) (A). Contrast enhanced SPGR demonstrated total occlusion of the Lt. distal vertebral artery.