Vascular Tortuosity May Be Associated With Cervical Artery Dissection

Bum Joon Kim, MD; Ewha Yang, MS; Na-Young Kim, MD; Mi-Jung Kim, MD; Dong-Wha Kang, MD; Sun U. Kwon, MD; Jong S. Kim, MD, PhD

Background and Purpose—Dissection is an increasingly recognized cause of ischemic stroke, which occurs spontaneously or after trauma, in relatively young patients. We hypothesized that there might be a predisposing factor weakening the vascular wall and that arterial tortuosity might be higher in patients with dissection.

Methods—We consecutively enrolled cervical artery dissection (CerAD) patients who had undergone magnetic resonance angiography. Age- and sex-matched healthy subjects who underwent magnetic resonance angiography in a routine health examination were used as controls. The tortuosity was measured semiautomatically from the carotid artery and vertebral artery (VA) arteries. Tortuosity index was defined as: [(arc/chord)−1×100] in each arteries. Independent risk factors associated with CerAD were investigated using multivariable analysis. Subgroup analysis according to the dissected artery was performed.

Results—There were no differences in vascular risk factors between the 75 CerAD patients and the 75 controls. The tortuosity indexes of the contralesional VA (16.3±6.8 versus 12.1±4.5, respectively; \(P<0.001\)) and carotid artery (8.8±4.0 versus 7.3±2.9, respectively; \(P=0.01\)) were higher in patients with CerAD compared with those of control subjects. VA tortuosity (odds ratio, 1.175; \(P=0.001\)) was independently associated with the presence of CerAD. In subgroup analysis, VA tortuosity was significantly higher in 57 patients with VA dissection than in controls (\(P<0.001\)), and carotid artery tortuosity was marginally higher in 18 patients with carotid artery dissection (\(P=0.05\)).

Conclusions—CerAD is associated with tortuous cervical arteries, which may implicate weakened cervical vascular structure in these patients. (Stroke. 2016;47:2548-2552. DOI: 10.1161/STROKEAHA.116.013736.)

Key Words: dissection ■ magnetic resonance angiography ■ risk factors ■ stroke ■ vertebral artery

Arterial dissection is an increasingly recognized cause of ischemic stroke, which mainly occurs in young and healthy individuals.\(^2\) Dissection may occur spontaneously or after a minor or major trauma.\(^3,4\) One of the postulated causes of arterial dissection is an underlying arteriopathy because of a predisposing connective tissue disease that weakens the arterial wall.\(^5\) Patients with connective tissue diseases with known genetic mutations show higher tortuosity in their arteries.\(^6,7\) Furthermore, a higher tortuosity index predicts the probability of arterial dissection development and overall outcomes in these patients.\(^8,9\) However, only a small proportion of patients with arterial dissection show a clinically overt connective tissue disorder.\(^10\) Nonetheless, even when there are no obvious signs of a connective tissue disorder, a weakened vascular structure may increase vasculature deformity in response to hemodynamic stress.\(^11\)

We hypothesized that tortuosity might be a surrogate for an underlying subclinical connective tissue weakness and be more prominent in patients with cervical artery dissection (CerAD) than in those without. Accordingly, we compared the tortuosity of cervical arteries in patients with CerAD to that of normal subjects.

Methods

Subjects

This study parallels a previously published study.\(^12\) Briefly, patients with ischemic stroke or transient ischemic attack who were admitted to Asan Medical Center (AMC) from March 2008 to February 2010 were prospectively registered. Among them, patients with ischemic stroke identified to have a dissection in their carotid artery (CA) or vertebral artery (VA) confirmed by appropriate imaging modalities were consecutively enrolled. Initially, patients were evaluated with magnetic resonance angiography (MRA) or computed tomographic angiography. Duplex sonography, high-resolution magnetic resonance imaging, or digital subtraction angiography was additionally performed to diagnose dissections.\(^13,14\) The detailed indications and findings of additional neuroimaging were described previously.\(^12\) Patients with poor quality MRA unsuitable for the measurement of vascular tortuosity or patients with only computed tomographic angiography data were excluded for technical reasons.

Age- and sex-matched controls were enrolled from individuals who underwent MRA in the Health Promotion Center of AMC.

Received April 10, 2016; final revision received June 30, 2016; accepted July 18, 2016.
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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.013736

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for the purpose of a routine health check-up during the same study period. If there were multiple subjects with an identical age and sex for 1 CerAD patient, the subject who underwent MRA on the closest date to the index patient was chosen as the control. Subjects with VA with a posterior inferior cerebellar artery ending were excluded because VA ending points were unknown and measurement of tortuosity was impossible (see below). The Institutional Review Board of AMC approved this study. Informed consent was waived because of the retrospective design.

Clinical Data
Vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking, were obtained from the prospectively registered database. The vascular risk factors of the controls were obtained from information obtained from the routine health examination. Hypertension was defined as the use of antihypertensive medication or blood pressure >140/90 mm Hg on repeated measurement. Diabetes mellitus was defined as the use of diabetes mellitus medication or fasting blood glucose >126 mg/dL or 2-hour plasma glucose >200 mg/dL. Hyperlipidemia was defined as the use of any lipid-lowering agent or a total cholesterol level >220 mg/dL or low-density lipoprotein cholesterol >130 mg/dL. Current smoking was defined as any smoking within 6 months before the event and was determined from the self-reported checklist.

A mechanical trigger event was regarded as significant if it occurred <1 month before the onset of the ischemia. These events included (1) any direct impact to the neck area, (2) any direct impact to the head with an indirect involvement of the neck, or (3) mechanical injury causing an extraordinary increase in intrathoracic or intra-abdominal pressure. Examples are whiplash injury, cervical manipulation therapy, and extreme head movements.3

Imaging Protocol
MRA was performed with a 1.5-T Magnetic Resonance Imaging unit (Signa; GE Medical Systems, Milwaukee, WI). Tortuosity was measured from the 3-dimensional (3D) contrast-enhanced MRA, which was performed after an intravenous bolus injection of 20 mL (3–4 mL/s) gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) with a relaxation time of 6 ms and an echo time of 1 ms. Angiographic images of 3D MRA were reconstructed using the maximum intensity projection algorithm. When the diagnosis obtained from conventional MRA was uncertain, additional high-resolution magnetic resonance imaging was performed with the use of an Achieva 3.0-T high-resolution magnetic resonance imaging scanner (Philips Healthcare, Eindhoven, The Netherlands). T1- and T2-weighted and proton density images were obtained. The major MR parameters of the proton density imaging were as follows: repetition time, 1000 ms; echo time, 20 ms; field of view, 200x200 mm; matrix size, 720x720; slice thickness, 1 mm; interslice gap, 0.5 mm; and average, 1.

Imaging diagnosis of CerAD was made with the modification of the previous criteria if one of the following findings was confirmed from any of the vascular imaging protocols: double lumen (the presence of a false lumen or an intimal flap), intramural hematoma, nonatherosclerotic tapered stenosis or occlusion, especially a flame-shaped or pearl-and-string sign or a dissecting aneurysm (pseudoaneurysm) at a nonbranching site. If bilateral dissection was suspected, the VA with a corresponding ischemic lesion was regarded as ipsilesional.

Measurement of the Cervical Artery Tortuosity
Vascular tortuosity was measured semiautomatically using a MATLAB-based program (R2015b; MathWorks Inc, Natick, MA). Tortuosity was measured in the dissected CA or VA and contralateral CA and VA of the CerAD patient and in the corresponding arteries of the age- and sex-matched control. In each subject, the anteroposterior view of 3D-reconstructed contrast-enhanced MRA was used (Figure 1A). The slice with the basilar tip nearest to the center of the bifurcation points of the middle cerebral artery and anterior cerebral artery on each side were used. Before measurement, the target vessel was manually outlined where the vessels cross each other (Figure 1B).

The program automatically segmented the vessel, distinguishing it from the background using k-means clustering (k=3). The extracted arteries were skeletonized using an open source code of the MATLAB package (Better Skeletonization; http://www.mathworks.com/matlabcentral/fileexchange/11123-betterskeletonization). Two points were then designated for the proximal and distal ends of the CA and VA. For the CA, the proximal end was the bifurcation point of the subclavian artery (or aorta in the left CA) and the distal end was the middle cerebral artery–anterior cerebral artery bifurcation point. For the VA, the proximal end was the bifurcation point of the subclavian artery and the distal end was the verteobasilar junction (Figure 1C). Tortuosity was automatically calculated by the program. The skeletonized length between the 2 points including all the natural curvatures was used as the arc length, and the Euclidian distance between the 2 points was used as the chord length. The tortuosity index was presented by a distant factor automatically calculated by the following formula: \(\frac{(arc\ length/chord\ length−1)\times 100}{\text{arc length/chord length}}\).9

Statistical Analysis
First, the demographic data, risk factors, and tortuosity of the CA and VA were compared between CerAD patients and age- and sex-matched controls. Independent risk factors for CerAD were investigated using a binary logistic analysis model. Because the tortuosity of the dissected CA and VA occasionally could not be measured, the tortuosity of the contralateral CA and VA was entered into the multivariable analysis model. In addition, the correlation between various factors and the vascular tortuosity was investigated using a multivariable linear regression model. The tortuosity of the contralateral CA and VA was compared between patients with intracranial and extracranial CerAD. Intracranial CerAD was defined as dissection occurring at the petrous, cavernous, or clinoid segments of the CA or the intradural segment of the VA.12 The values were also compared between patients with and without a history of trauma.

Second, an identical analysis was performed in subgroups of patients with dissection in the CA and VA. The \(\chi^2\) test and Student t
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Table 1. Comparison Between Patients With Cervical Artery Dissection and Age- and Sex-Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>Cervical Artery Dissection Patients (n=75)</th>
<th>Age- and Sex-Matched Controls (n=75)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.6 [12.9]</td>
<td>44.6 [12.9]</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>59 (78.7)</td>
<td>59 (78.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (32.0)</td>
<td>16 (21.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (5.3)</td>
<td>8 (10.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19 (25.3)</td>
<td>14 (18.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Current smoking</td>
<td>31 (41.3)</td>
<td>27 (36.0)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Vascular tortuosity

<table>
<thead>
<tr>
<th></th>
<th>Carotid artery</th>
<th>Vertebral artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted</td>
<td>8.8 [4.0]</td>
<td>16.3 [6.8]</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>7.3 [2.9]</td>
<td>12.1 [4.5]</td>
</tr>
<tr>
<td>(P) value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as a number (% column) or mean [SD]. Tortuosity is presented by distant factor ([arc length/chord length−1]×100).

Table 2. Independent Factors Associated With Cervical Artery Dissection

<table>
<thead>
<tr>
<th></th>
<th>Crude OR (95% CI)</th>
<th>(P) Value</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted (P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.735 (0.832–3.620)</td>
<td>0.142</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.472 (0.136–1.640)</td>
<td>0.237</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.478 (0.678–3.224)</td>
<td>0.328</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.253 (0.648–2.420)</td>
<td>0.503</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Carotid artery tortuosity</td>
<td>1.155 (1.027–1.298)</td>
<td>0.016</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Vertebral artery tortuosity</td>
<td>1.175 (1.088–1.269)</td>
<td>&lt;0.001</td>
<td>1.175 (1.088–1.269)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The adjusted odd ratio and \(P\) value represent the results of binary logistic regression analysis. CI indicates confidence interval; and OR, odds ratio.

Results

During the study period, 125 patients with ischemic stroke because of CerAD were identified. Of these, 85 patients had VA (n=65) or CA (n=20) dissection. Ten patients were excluded because they were evaluated by computed tomographic angiography only (n=8) or had poor-quality MRA (n=2). Finally, 75 patients with CerAD were analyzed (57 patients with VA dissection and 18 patients with CA dissection). The mean age of these patients was 44.6±12.9 years and 59 (78.7%) were male. Eight patients (6 VA dissections and 2 CA dissections) had suspected bilateral dissection. None of the patients were diagnosed as having an overt connective tissue disorder.

The tortuosity of the contralesional CA and VA was measured in all patients. In contrast, the tortuosity could be measured in only 20 of the 57 VA dissections (38.4%) and 5 of the 18 CA dissections (27.8%) that were traceable on MRA. The tortuosity could not be measured in the remaining cases because the dissected portion was not traceable on the MRA due to severe stenosis or occlusion. Among the 57 patients with VA dissection, 29 (50.9%) were located in the extracranial portion of the VA; the remainder were located in the intracranial portion. Most CA dissections (13 patients; 72.2%) were located in the extracranial portion of the CA.

Vascular Tortuosity of Patients With CerAD

There were no differences in vascular risk factors between patients with CerAD and age- and sex-matched healthy controls (Table 1). The tortuosities of cervical arteries were higher in those with CerAD than the controls: the contralesional VA (16.3±6.8 versus 12.1±4.5, respectively; \(P<0.001\)) and CA (8.8±4.0 versus 7.3±2.9, respectively; \(P=0.01\)). By multivariate analysis, the vascular tortuosity of the VA (odds ratio, 1.175; 95% confidence interval [CI], 1.088–1.269; \(P=0.001\)) was independently associated with the presence of CerAD (Table 2). In addition, the dissected VA (in measurable patients, n=20) was more tortuous than that of the corresponding VA of the controls (18.2±5.8 versus 11.8±4.0, respectively; \(P<0.001\)). There was no significant difference between the dissected VA and the contralesional VA (18.2±5.8 versus 16.8±5.4, respectively; \(P=0.43\)).

The linear regression analysis results demonstrated that the VA tortuosity were independently associated with age (\(\beta=0.142, 95\%\) CI for \(\beta=0.075–0.209; P<0.001\)), female sex (\(\beta=3.378, 95\%\) CI for \(\beta=1.280–5.476; P=0.002\)), and presence of CerAD (\(\beta=4.216, 95\%\) CI for \(\beta=2.522–5.909; P<0.001\)). Similarly, the factors associated with CA tortuosity were age (\(\beta=0.887, 95\%\) CI for \(\beta=0.454–0.129; P<0.001\)), female sex (\(\beta=1.408, 95\%\) CI for \(\beta=1.353–2.681; P=0.030\)) and the presence of CerAD (\(\beta=1.271, 95\%\) CI for \(\beta=0.243–2.298; P<0.016\)).

There was no difference in the tortuosity of the cervical arteries between intra- and extracranial CerAD (VA tortuosity: 16.4±5.8 versus 16.2±7.6, \(P=0.89\) and CA tortuosity: 8.8±3.2 versus 8.8±4.1, \(P=0.99\), respectively) or according to the presence of trauma history (VA tortuosity: 17.1±6.2 versus 16.0±7.1, \(P=0.54\) and CA tortuosity: 8.8±3.8 versus 8.8±4.1, \(P=0.99\), respectively).

Subgroup Analysis According to the Dissected Artery

Among the 57 patients with VA dissection, there were no differences in terms of vascular risk factors compared with the age- and sex-matched controls. The tortuosity of the VA was significantly higher in patients with VA dissection than in controls (16.8±7.3 versus 11.9±4.0, respectively; \(P<0.001\); Table 3; Figure 2A). After adjusting for potential confounders, VA...
tortuosity (odds ratio, 1.267; 95% CI, 1.116–1.438; \( P < 0.001 \)) and hypertension (odds ratio, 3.765; 95% CI, 1.304–10.874; \( P = 0.01 \)) were independently associated with VA dissection.

Among the 18 patients with CA dissection, there were no significant differences in terms of vascular risk factors compared with controls. The tortuosity of the VA did not differ between patients with CA dissection and controls (14.5±4.9 versus 12.7±5.7, respectively; \( P = 0.30 \)), whereas the tortuosity of the CA was marginally higher in patients with CA dissection than that of controls (10.2±5.9 versus 7.4±1.6, respectively; \( P = 0.05 \); Table 3; Figure 2B). However, the association was not significant by multivariate analysis after adjusting for potential confounders (odds ratio, 1.427; 95% CI, 0.924–2.205; \( P = 0.109 \)).

**Discussion**

In our cross-sectional case-control study, the tortuosity of the dissected VA and contralesional VA and CA was higher in patients with CerAD than in age- and sex-matched controls. The tortuosity of the contralesional VA was independently associated with CerAD. The tortuosity of the VA and CA was not different between patients with intracranial and extracranial dissection.

Our current results are consistent with those of previous reports showing that a higher arterial tortuosity index of the aorta and VA was an independent predictor of arterial dissection in patients with Marfan syndrome.\(^8^,^9\) Arterial kinking and coiling were also found to be associated with the development of CA dissection.\(^1^5^,^1^6\) Furthermore, high coronary artery tortuosity has been associated with coronary artery dissections and with extracoronary vasculopathies, such as peripheral artery dissections.\(^1^7^,^1^8\) Therefore, a predisposing systemic factor may weaken the arterial wall, ultimately leading to increased vascular tortuosity and arterial dissection after certain provoking events. Indeed, several studies demonstrated systemic ultrastructural abnormalities in various tissues of

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**Table 3. Comparison Between Patients With Vertebral and Carotid Artery Dissection and Age- and Sex-Matched Controls**

<table>
<thead>
<tr>
<th></th>
<th>Vertebral Artery Dissection (n=57)</th>
<th>Carotid Artery Dissection (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dissection</td>
<td>Control</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.7 [12.1]</td>
<td>44.4 [15.4]</td>
</tr>
<tr>
<td>Male</td>
<td>43 (75.4)</td>
<td>16 (88.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (35.1)</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (7.0)</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>16 (28.1)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>27 (47.4)</td>
<td>19 (33.3)</td>
</tr>
<tr>
<td>Vascular tortuosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid artery</td>
<td>8.3 [3.1]</td>
<td>7.3 [3.2]</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>16.8 [7.3]</td>
<td>11.9 [4.0]</td>
</tr>
</tbody>
</table>

Results are expressed as a number (% column) or mean [SD]. Tortuosity is presented as the distant factor ([arc length/chord length−1]×100).

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**Figure 2. Tortuosity of arteries of patients with vertebral (VA; A) and carotid artery dissection (CA; B) and age- and sex-matched controls.** \(^* P<0.05.\)
CerAD patients in the absence of overt clinical signs of connective tissue disease.\textsuperscript{19,20} However, it is still unclear how the side of dissection is determined. According to our results, not only the dissected cervical artery itself but also the contralateral normal-looking cervical artery was more tortuous than the vessels on the corresponding side of normal controls. Furthermore, the dissected cervical artery was not more tortuous than the contralateral normal-looking cervical arteries (Figure 2). Therefore, the side of the dissection might be determined by the site of traumatic injury, rather than the degree of arterial tortuosity. However, because the side of trauma was not specifically investigated, and the number of dissected vessels whose tortuosity could be measured was small, our findings should be interpreted with caution.

It is well known that there are differences between CA and VA dissections.\textsuperscript{21} From our subgroup analysis, we found that the tortuosity of the VA (either ipsilateral or contralateral), but not that of CA, was significantly higher than that of normal controls in patients with VA dissection. Similarly, the tortuosity of the CA, but not that of VA, was marginally higher in patients with CA dissection. Therefore, there may be site specificity in the tortuosity of cervical arteries that results in dissection in the same arterial group (Table 3). These findings may at least, in part, explain the clustering of dissection occurring at the same type of artery, rather than involving both VA and CA, in patients with multiple dissection.\textsuperscript{22}

Our current study has several limitations. First, the number of patients was small and some of our results were thus underpowered, especially those of the subgroup analysis. Second, we only enrolled arterial dissection patients who presented with ischemic stroke. Therefore, our findings may not be generalizable to CerAD patients presenting with hemorrhage or isolated headache. Third, we analyzed the tortuosity based on the 2D images of the anteroposterior images of 3D-reconstructed MRA. Three-dimensional analysis of the 3D vascular tortuosity might strengthen our results. Finally, the eventual cause of the increased tortuosity could not be verified by our current analysis, due to the lack of pathology findings. Further studies with a larger number of patients that involve biomolecular or genetic studies are needed to better understand the pathogenesis of arterial dissection. Nevertheless, our current data suggest that CerAD may be associated with a weakened vascular structure, evidenced by higher tortuosity of the VA and CA.

**Sources of Funding**

This study was supported by a grant from the Ministry for Health, Welfare, and Family Affairs, Republic of Korea (HI14C1985).

**Disclosures**

None.

**References**

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Stroke. 2016;47:2548-2552; originally published online August 16, 2016;
doi: 10.1161/STROKEAHA.116.013736

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