Arterial Tortuosity: An Imaging Biomarker of Childhood Stroke Pathogenesis?

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Background and Purpose—Arteriopathy is the leading cause of childhood arterial ischemic stroke. Mechanisms are poorly understood but may include inherent abnormalities of arterial structure. Extracranial dissection is associated with connective tissue disorders in adult stroke. Focal cerebral arteriopathy is a common syndrome where pathophysiology is unknown but may include intracranial dissection or transient cerebral arteriopathy. We aimed to quantify cerebral arterial tortuosity in childhood arterial ischemic stroke, hypothesizing increased tortuosity in dissection.

Methods—Children (1 month to 18 years) with arterial ischemic stroke were recruited within the Vascular Effects of Infection in Pediatric Stroke (VIPS) study with controls from the Calgary Pediatric Stroke Program. Objective, multi-investigator review defined diagnostic categories. A validated imaging software method calculated the mean arterial tortuosity of the major cerebral arteries using 3-dimensional time-of-flight magnetic resonance angiographic source images. Tortuosity of unaffected vessels was compared between children with dissection, transient cerebral arteriopathy, meningitis, moyamoya, cardioembolic strokes, and controls (ANOVA and post hoc Tukey). Trauma-related versus spontaneous dissection was compared (Student t test).

Results—One hundred fifteen children were studied (median, 6.8 years; 43% women). Age and sex were similar across groups. Tortuosity means and variances were consistent with validation studies. Tortuosity in controls (1.346±0.074; n=15) was comparable with moyamoya (1.324±0.038; n=15; P<0.998), meningitis (1.348±0.052; n=11; P<0.989), and cardioembolic (1.379±0.056; n=27; P<0.190) cases. Tortuosity was higher in both extracranial dissection (1.404±0.084; n=22; P<0.021) and transient cerebral arteriopathy (1.390±0.040; n=27; P<0.001) children. Tortuosity was not different between traumatic versus spontaneous dissections (P=0.70).

Conclusions—In children with dissection and transient cerebral arteriopathy, cerebral arteries demonstrate increased tortuosity. Quantified arterial tortuosity may represent a clinically relevant imaging biomarker of vascular biology in pediatric stroke. (Stroke. 2016;47:1265-1270. DOI: 10.1161/STROKEAHA.115.011331.)

Key Words: arterial tortuosity ■ child ■ dissection ■ magnetic resonance angiography ■ pediatric stroke ■ stroke

A rteriopathy is the leading cause of childhood arterial ischemic stroke (AIS) and its recurrence.1,2 Outcomes are poor with most survivors having lifelong disability. Mechanisms are poorly understood, limiting treatment and prevention strategies. The most common syndrome is a unilateral stenotic arteriopathy of the internal, middle, and anterior cerebral artery trifurcation; the term focal cerebral arteriopathy (FCA) of childhood has been coined to describe this imaging appearance in children. The differential diagnosis for FCA includes transient cerebral arteriopathy (TCA), a presumed inflammatory arteriopathy that can have distinct angiographic features (like arterial banding) and by definition has a monophasic natural history.3 Intracranial dissection has also been suggested as a mechanism for FCA with supportive evidence, including possible associations between childhood AIS and trauma, a lack of inflammatory biomarkers, and small pathological series demonstrating dissection in FCA cases.4

An improved understanding of the vascular biology underlying childhood cerebral arteriopathy is essential to develop treatment strategies and to improve outcomes. Large and medium cerebral arteries are inaccessible to pathological examination; however, radiographic imaging of arteriopathy is an alternative, rapidly evolving approach to assessing arterial properties in vivo.5 A growing number of associations between childhood arteriopathies and congenital, genetic syndromes further support a role for inherent abnormalities of the
cerebral arteries in childhood AIS pathogenesis. Abnormal arterial structure marked by having more kinks, twists, and loops can be described as more tortuous. Arterial tortuosity is highly variable and known to be increased in a variety of genetic connective tissue disorders (eg, Menke disease and Loey–Dietz syndrome). A recent adult stroke study using standardized visual categorization of cervical arterial tortuosity found an association with extracranial dissection. However, computer-assisted analysis of magnetic resonance angiograms (MRAs) may afford more sensitive and objective quantifications of arterial tortuosity and has been used to demonstrate associations with hypertension and other adult cerebrovascular conditions.

Arterial tortuosity has not been investigated in childhood AIS and may represent a window into inherent vascular structure and biology. We hypothesized that arterial tortuosity (of vessels that seem unaffected on standard vascular imaging) is increased in children with stroke because of arterial dissection compared with those with stroke because of other causes or control children.

Materials and Methods

Population
This was a substudy of the Vascular Effects of Infection in the Pediatric Stroke (VIPS) study, the complete methodology of which is described elsewhere. VIPS was a prospective, multicenter study of childhood AIS. Children recruited were aged 1 month to 18 years with magnetic resonance imaging–confirmed acute AIS. VIPS collected extensive infectious histories obtained through parental interview, blood and serum samples (and cerebrospinal fluid, when clinically obtained), and standardized brain and cerebrovascular imaging. Importantly, all imaging was reviewed and classified by both the site investigator and additional centralized, multiple, expert, blinded raters. Using standardized criteria, each case was first classified by the central review committee into 1 of 3 mutually exclusive diagnostic categories: definite, possible, or no arteriopathy. Those with arteriopathy were then further classified as having secondary diagnoses, including arterial dissection (spontaneous and traumatic), TCA, moyamoya, and secondary vasculitis (including meningitis). The level of certainty on the secondary diagnosis was also assigned. Cases with no arteriopathy were further classified as having cardioembolic, other known cause, or idiopathic. For this substudy, we included only those subjects with the highest level of certainty on their diagnostic category: those classified as definite arteriopathy and with a secondary diagnosis classified with high certainty, as well as a subgroup of children with no arteriopathy and cardioembolic stroke. The original, anonymized DICOM files of all eligible subjects were obtained directly from the central VIPS imaging repository for analysis.

Controls
To determine normative values for childhood craniocervical arterial tortuosity, MRA studies completed on children from the same age range were obtained from the Alberta Children’s Hospital Pediatric Neuroimaging Database in accordance with previously approved methods. Criteria were (1) age 29 days to 18 years, (2) cerebral time-of-flight MRA completed between 2005 and 2013 (same scanner and protocol requirements as VIPS sites) and reported as normal, and (3) no history of stroke, cerebral or systemic arterial or connective tissue disease, or recent trauma. All control scans were completed on a 1.5-T Siemens Avanto magnetic resonance imaging scanner (Siemens Medical Systems, Erlangen, Germany). Both the VIPS study and this substudy were approved by the institutional Research Ethics Board.

Arterial Tortuosity Quantification
We used a previously validated methodology using ImageJ software to analyze and quantify arterial tortuosity. Our technique was similar to that previously described with slight modifications as follows. First, each subject’s cerebral arteries were isolated from their 3-dimensional (3D) time-of-flight MR angiographic source images in DICOM format. The imaging studies of the highest quality closest to stroke diagnosis was used. Segments with focal disease (eg, TCA and dissection) were not included. The algorithm iterates through each 2D source image slice in the 3D space, calculates the center of mass point (single voxel) for each cross section of an arterial lumen, and crops the rest of the local area. These center points are connected to form centerlines that make up an isolated skeleton structure of the arteries. Local and global arterial structure is maintained, including bifurcations (Figure 1).

Tortuosity was then calculated for each individual artery by dividing the path length by the Euclidean (shortest) distance between its end points; this value is referred to as the distance factor metric (DFM). The software does not distinguish arteries from one another, so each arterial segment was manually defined by selecting 2 end points. A limitation in previous studies was analyzing the internal carotid and vertebral arteries as they descend down the neck lacking clearly definable end points. Selection of the end point to define the artery of interest may bias the DFM calculation (Figure 1). To address this, our methodology is designed to only require 1 definite end point, such as the convergence of the vertebral arteries or bifurcation point of the internal carotid artery at the circle of Willis. The second end point must still be placed in roughly the same area for comparable results, but the margin for error is much greater. The software then iterates through each voxel along the centerline. At each voxel, the path length and Euclidian distance are calculated between it and the first end point generating a local DFM. After iterating through all the voxels in 3D, the final tortuosity score assigned to an artery is the maximum DFM generated. This choice of using maximum DFM was made based on previously validated methods.

This process was repeated for each of the following major cerebral arteries: basilar, left and right vertebral, left and right internal carotids, and the M1 segments of the left and right middle cerebral arteries. Anterior cerebral and further order branches were beyond the resolution of the method. The most caudal slices available were used, resulting in vertebral and internal carotid artery imaging to the midcervical level. In subjects with diagnosed arteriopathy, the affected arterial segments were not included in the tortuosity measurements. Primary outcome was the tortuosity score, calculated as the mean maximum DFM of the 7 arteries in each subject.

Analysis and Sample Size
After confirmation of a normal distribution, the relative tortuosity of each major artery was compared using ANOVA with post hoc Tukey test. A paired t test compared relative symmetry between left and right for all paired vessels within subjects. Differences in mean tortuosity across control and disease groups were compared using

Figure 1. Tortuosity measurement. The distance factor metric was calculated to quantify relative tortuosity. Dashed arrows represent Euclidian distances (d) to local points along artery path length (L). Distance factor metric (DFM)=L/d. Using a bifurcation point as the definite start, an iteration is performed through every voxel along the path calculating a local DFM until the end point is reached.
Table. Demographic Characteristics of Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Sex, M:F</th>
<th>Age (mean±SD), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15</td>
<td>10:5</td>
<td>6.25±5.90</td>
</tr>
<tr>
<td>Dissection</td>
<td>22</td>
<td>13:9</td>
<td>9.51±6.27</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>15</td>
<td>8:7</td>
<td>6.12±4.46</td>
</tr>
<tr>
<td>Meningitis</td>
<td>11</td>
<td>7:4</td>
<td>3.83±5.22</td>
</tr>
<tr>
<td>TCA</td>
<td>25</td>
<td>11:14</td>
<td>9.67±4.42</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>27</td>
<td>16:11</td>
<td>7.38±6.28</td>
</tr>
</tbody>
</table>

Typically developing controls were comparable with all childhood arterial ischemic stroke disease groups except that the average age was lower in the meningitis group. F indicates female; M, male; and TCA, transient cerebral arteriopathy.

ANOVA (post hoc Tukey). Tortuosity of traumatic versus atraumatic dissection cases was compared with a Student t test (means) and a Levene test (variance). A blinded intrarater analysis before study initiation confirmed highly reproducible mean and segmental tortuosity measurements (all intraclass correlations, >0.96). On the basis of typical means and variances from previous adult data using similar measures,12 a significant increase of 1SD in dissection subjects, and α = 0.05, our sample of convenience from the VIPS study was 94% powered to address the primary hypothesis.

Results

Of the 480 subjects enrolled in the VIPS study, 100 (21%) satisfied inclusion criteria for this substudy. Excluded case demographics did not differ from the study sample. The characteristics of the study population (including 15 controls) divided by the group are summarized in the Table. Age and sex were comparable across groups.

Representative examples across the spectrum of tortuosity observed are shown in Figure 2. Differences in tortuosity were not readily apparent on visual inspection of the original MRA images.9 Tortuosity scores were normally distributed in all groups. Controls (93% imaged for headaches) demonstrated an average tortuosity score of 1.333 (median, 1.331) with a range of 1.283 to 1.443. Average values, ranges, and variance seemed comparable with previously published values in adults.9

Across all subjects, average tortuosity varied among the different arterial segments (P<0.0001; Figure 3). Consistent with expected anatomic differences, the internal carotid had the highest values, whereas basilar scores were lower. Tortuosity scores were symmetrical with comparable values between left and right measures of paired arteries. Tortuosity scores were not associated with age or sex (Figure 4).

Differences in mean tortuosity were observed across disease groups (P<0.001; Figure 5). Variability around this number was low with an SD of 0.039. On the basis of control measures, the fifth and 95th percentiles for tortuosity were 1.28 to 1.44. Variance of tortuosity was also greater in dissection (P=0.017) and TCA (P=0.042) groups compared with controls but not compared with the other disease groups.

Compared with controls, tortuosity was higher in both dissection (1.398±0.072; P=0.021) and TCA (1.421±0.076; P=0.001) groups. Tortuosity scores were not different from controls for the remaining stroke disease groups: moyamoya (1.324±0.038; P=0.998), meningitis (1.348±0.052; P=0.989), and cardioembolic (1.379±0.056; P=0.190). Within the dissection group, mean tortuosity between traumatic (1.391±0.036) and spontaneous (1.403±0.090; P=0.671) were not different although variance was higher in the spontaneous group (P=0.018).

Discussion

Our findings suggest that arterial tortuosity is different in children with certain forms of arteriopathic stroke, specifically dissection and TCA. Tortuosity seems to be accurately measurable from clinically obtained MRA in children. Arterial tortuosity may represent an imaging biomarker of inherent vascular biology with implications for understanding the pathophysiology of childhood stroke.

Inherent arterial structure plays a role in specific cerebrovascular diseases at all ages. The number of genetic connective tissue diseases responsible for cerebral arteriopathies continues to grow, such as collagen 4A1 and A2, Majewski Osteodysplastic Primordial Dwarfism Type 2 (MOPD2), and smooth muscle actin (ACTA2).6,13,14 That many of these begin early in life and are accompanied by complications throughout the arterial tree and other organs attests to the importance of inherent arterial stability in long-term health. In adult stroke caused by dissection, evidence of connective tissue alterations is well established, including a large proportion of otherwise asymptomatic patients with evidence of disordered collagen, elastin, or other connective tissue elements visible on skin electron microscopy.15,16 A recent adult stroke study described an association between visually classified tortuosity and dissection.5 Linking these pathological and genetic findings with...
such readily recognizable imaging biomarkers, such as arterial tortuosity, could facilitate the earlier assignment of likely mechanism and appropriate management in children with stroke.

The TCA syndrome is a well-established imaging syndrome, but its pathophysiology has emerged as one of the most perplexing and controversial issues in childhood stroke. Its clinical radiographic characteristics are often indistinguishable from other forms of FCA although we used the best available consensus imaging criteria for classification. Observations of limited, weak epidemiological associations with remote infections and lack of laboratory or imaging biomarkers of inflammation have reasonably questioned the grounds for a primary infectious or inflammatory mechanism. Our finding that the mean tortuosity is different in children with TCA brings a fundamental new consideration to trying to understand the biological mechanisms of the disease. That the inherent structural properties of the cerebral arteries should predispose one specific section to an acquired infectious or inflammatory process seems unlikely.

Could TCA be mainly because of intracranial dissection? Despite much interest and reasonable theory for an inflammatory, possibly parainfectious mechanism to TCA, definitive proof has been lacking. Transient, abnormal serum biomarkers of disordered inflammation have been described in a small case series of children with TCA when compared with those with cardioembolic stroke. Another small case series described 3 children with clinically diagnosed TCA/FCA who died and went to autopsy where pathological evidence of intracranial dissection (and no evidence of inflammation) was described. It should also be noted that these 2 possibilities are also not mutually exclusive (eg, an artery damaged by acute inflammation might well be vulnerable to dissection).

Our findings that TCA and dissection share a similar degree of increased tortuosity at regional/distant sites to the pathology that differentiates them from both controls and other childhood AIS subtypes do not prove that TCA is intracranial dissection. They do raise serious consideration that the inherent structure of the artery itself may be a key component of the mechanism that underlies the disease.

Our technique provides a straightforward method of objectively quantifying abnormality in arterial structure. However, several methodological issues are identified. Because this was a multicenter study where different MR scanners were used, not all imaging was standardized. Some imaging data from sites were unusable or incompatible with the software. The software method might also be improved when calculating the centerline for an artery. The 3D time-of-flight MRA source images still contained voxel information from the skull, which, in some cases, added noise possibly interfering with the centerline calculations. Signals from the anterior cerebral artery imaging were too weak to be analyzed.
Increasing computational power available and improvements in the algorithm may increase our ability to capture smaller vascular structures. In our study, tortuosity scores were assigned by averaging the tortuosity score of each major artery. However, it is possible that specific arteriopathies affect specific arteries differently.

Conclusions

Arterial tortuosity is measurable in children with stroke and may represent a clinically relevant imaging biomarker of vascular biology in pediatric stroke. Children with dissection have increased arterial tortuosity, and no difference was found in traumatic and spontaneous dissection. Whether this reflects inherent abnormalities of arterial structure requires further study. Children with the TCA syndrome also seem to have higher tortuosity. This provides indirect support of previous suggestions that some TCA cases are intracranial dissections.

Appendix: Vascular Effects of Infection in Pediatric Stroke Investigators

Dowling MM (University of Texas Southwestern Medical Center, Dallas), Benedict SL (Primary Children’s Medical Center, Salt Lake City, UT), Bernard TJ (Children’s Hospital Colorado, Aurora), Fox CK (University of California San Francisco), deVeber GA (The Hospital for Sick Children, Toronto, ON), Friedman NR (Cleveland Clinic Children’s Hospital, OH), Lo WD (The Ohio State University and Nationwide Children’s Hospital, Columbus), Ichord RN (Children’s Hospital of Philadelphia, PA), Tan MA (University of the Philippines-Philippine General Hospital, Manila, Philippines), Mackay MT (Royal Children’s Hospital Melbourne, Melbourne, Victoria, Australia), Kirton A (Alberta Children’s Hospital, Calgary, Alberta, Canada), Hernandez Chavez MI (Pontificia Universidad Catolica de Chile, Santiago, Chile), Humphreys P (Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada), Jordan LC (Vanderbilt University Medical Center, Nashville, TN), Sultan SM (Columbia University Medical Center, New York, NY), Rivkin MJ (Boston Children’s Hospital, MA), Rafay MF (Children’s Hospital, Winnipeg, University of Manitoba, Winnipeg, Manitoba, Canada), Titomanlio L (Hôpital Robert Debré, Paris, France), Kovacevic GS (Mother and Child Healthcare Institute, Beograd, Serbia), Yager JY (Stollery Children’s Hospital, Edmonton, Alberta, Canada), Amylie-Lefond C (Seattle Children’s Hospital, WA), Dalmini N (Evelina London Children’s Hospital, London, United Kingdom), Condie J (Phoenix Children’s Hospital, AZ), Yeh EA (Children’s Hospital of Buffalo, NY), Kneen R (Alder Hey Children’s Hospital, Liverpool, United Kingdom), Bjornson BH (British Columbia Children’s Hospital, Vancouver, British Columbia, Canada), Pergami P (West Virginia University, Morgantown), Zou LP (Chinese PLA General Hospital, Beijing, China), Elbers J (Stanford Children’s Health, Palo Alto, CA), Abdalla A (Akron Children’s Hospital, OH), Chan AK (McMaster University Medical Center, Hamilton, Hamilton, Ontario, Canada), Farooq O (Women & Children’s Hospital of Buffalo, NY), Lim MJ (Evelina London Children’s Hospital, London, United Kingdom), Carpenter JL (Children’s National Medical Center, Washington, DC), Pavlakis S (Maimonides Medical Center, Brooklyn, NY), Wong VCN (Queen Mary Hospital, the University of Hong Kong, Hong Kong), Forsyth R (Institute of Neuroscience, Newcastle University, Newcastle, United Kingdom).

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Disclosures

None.

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动脉迂曲: 儿童卒中病因的影像学标志物?

Arterial Tortuosity: An Imaging Biomarker of Childhood Stroke Pathogenesis?

Felix Wei; Karl T. Diedrich, PhD; Heather J. Fullerton, MD, MAS; Gabrielle deVeber, MD, MSc; Max Wintermark, MD, MAS; Jacquie Hodge, MSc; Adam Kirton, MD, MSc; and the Vascular Effects of Infection in Pediatric Stroke (VIPS) Investigators

背景和目的: 动脉病是儿童期动脉缺血性卒中的首要原因，其发病机制不明，动脉结构的先天性异常是可能的原因之一。成人卒中中，颅外动脉夹层与结缔组织病关系密切。尽管局灶性脑动脉病的病理生理学尚不明确，但可能的原因包括颅内动脉夹层及短暂性脑动脉病等。本研究通过对比儿童缺血性卒中中动脉迂曲进行量化分析，验证动脉夹层患儿中动脉迂曲的比例增加。

方法: 儿童卒中感染对血管的影响 (Vascular Effects of Infection in Pediatric Stroke, VIPS) 研究招募年龄在 1 至 18 岁的患有缺血性卒中的儿童，对照组来自卡尔加里儿童卒中项目。多组研究者客观进行诊断标准的制定。使用经验证的影像软件计算通过三维时间飞跃法磁共振血管造影序列呈像的颅内大血管的平均动脉迂曲度。比较有动脉夹层、短暂性脑动脉病、脑膜炎、脑梗死及心源性卒中的患儿和对照组的非受累血管迂曲度（使用 ANOVA 及 post hoc Tukey 法）。同时比较创伤相关动脉夹层及自发的动脉夹层的动脉迂曲度（t 检验）。

结果: 对照组 (1.346±0.074; n=15) 相比患有烟雾病 (1.324±0.038; n=15; P=0.998)、脑膜炎 (1.348±0.052; n=11; P=0.989) 及心源性卒中 (1.379±0.066; n=27; P=0.190) 的病例组动脉迂曲度无统计学差异。在患有颅外动脉夹层 (1.404±0.04; n=22; P=0.021) 及短暂性脑动脉病 (1.390±0.040; n=27; P=0.001) 的患者中，动脉迂曲度高于对照组。在患有自发性动脉夹层和外伤相关性动脉夹层患者之间，动脉迂曲度无差异（P=0.70）。

结论: 在患有动脉夹层和短暂性脑动脉疾病的儿童中，动脉迂曲增加。量化的动脉迂曲度可能是儿童卒中血管生物学的临床影像学标志物。

关键词: 动脉迂曲; 儿童; 夹层; 磁共振血管造影; 儿童卒中; 卒中

(Stroke. 2016;47:1265-1270. 郑州大学第一附属医院神经内科 高远 译 许予明 校)
动脉迂曲量化

该研究采用已经证实的方法，应用 Image J 软件来分析和量化动脉迂曲。我们的技术与之前描述的相似，但略有修改。首先，将所有纳入患者的脑动脉影像以 DICOM 格式，从三维时间飞跃法 MRA 影像中获取。该研究应用高密度影像学标准来判断血管疾病中的病变节段。通过在三维空间中每两个二维源图像切片的迭代计算，计算每段动脉管腔的横截面和其他原位区域的质点(单体素)，这些中心点连接以形成中心线上的动脉的分离的骨架结构。从而获得包括分叉处在内的局部和整体动脉结构(图 1)。

动脉迂曲度是该动脉的总长度与两端点间的欧氏距离(最短)的比值，这个值叫做距离测量标准值(distance factor metric, DFM)。ImageJ 软件不能自动区分不同的动脉，所以对于每段动脉需要人为的手动选择 2 个端点。由于颈内动脉和椎动脉沿颈部下行，缺乏明确的定位标志点，故该软件对其的判定有一定的局限性。动脉端点的选择会影响 DFM 的计算结果(图 1)。考虑到这一局限性，我们只需要明确 1 个端点。如椎动脉的汇集点或 Willis 环内动脉的分岔点。第二个端点必须放在大致相同的区域，否则会产生较大误差。ImageJ 软件循环处理中心线上的每个小单位，依据总长度和欧式距离可计算出该位置的 DFM 值。依次计算出此空间内所有小单位的 DFM 值，拥有最大 DFM 值的动脉，此 DFM 值即为该动脉的迂曲度。这种把最大 DFM 值作为迂曲度的方法已在之前的研究中验证。

对于一些主要的脑动脉：如基底动脉、双侧椎动脉、双侧颈内动脉和双侧大脑中动脉的 M1 段，我们可以重复以上测量过程。但对大脑前动脉及其分支不适用。最边缘至中颈段水平，可使椎动脉和颈内动脉显影。对于已诊断为动脉病变的患者，动脉的病变段不进行迂曲度的测量。主要结果是迂曲度的评分(患者 7 条动脉最大的 DFM 的平均值作为该患者最终的弯曲度结果)。

数据分析及样本容量

每根主要动脉的相对迂曲度确认服从正态分布后，通过 ANOVA 进行分析。
检验（post hoc Tukey 法）进行比较分析。受试者之间所有配对血管左右两侧通过配对 t 检验分析。使用方差分析（post hoc Tukey 法）对比对照组和疾病组平均迂曲度的不同。创伤性和非创伤性夹层患者各组人群的血管迂曲度采用 t 检验(平均值)和方差齐检验(方差)方法分析。评估者内的单盲分析得出，评估者间对迂曲度的平均值和节段性评估方面有高度重复性(所有组内相关性 > 0.96)。使用类似的方法得出，夹层患者在之前成人的数据基础上明显增加了 1 个标准差，且 α=0.05。我们的样本容量占 VIPS 研究的 94%，有力的证明了我们的最初的假设。

结果

在 VIPS 研究纳入的 480 例患者中，100 例患者(21%)符合该亚组试验的纳入标准。未纳入的患者与纳入患者人口基线资料无统计学差异。各组人群(包括 15 例对照人群)之间的性别、年龄对比情况及特点，如表格所示。

迂曲度的典型例子如图 2 所示。血管弯曲度的差异在原始 MRA 图像的肉眼观察下并不是显而易见的。各组之间迂曲度评分的符合正态分布。对照组(93% 的图像为头痛患者)迂曲度得分的平均值为 1.333（中间值，1.331），得分在 1.283 与 1.443 之间。平均值、范围和差异与之前公布的成人的数值相一致。

该研究中，不同动脉血管间的平均弯曲度存在差异 (P < 0.0001; 图 3)。与基底动脉相比，颈内动脉弯曲度得分明显较高，这与两侧解剖特点的不同是相一致的。左右半球成对的血管弯曲度得分是基本对称的（如左侧大脑中动脉 M1 段与右侧大脑中动脉 M1 段得分基本一致）。弯曲度与年龄性别无关（图 4）。

不同分组间的弯曲度均值是不同的（P < 0.001; 图 5）。弯曲度的变异性较低，其标准差为 0.039。在控制测量误差的基础上，弯曲度 5% 百分位点和 95% 百分位点分别在 1.28 和 1.44。与对照组相比，解剖组 (P=0.017) 和 TCA 组的 (P=0.042) 弯曲度变化较大，但在其他组未得出该结果。

与对照组相比，解剖组 (1.398 ± 0.072; P=0.021) 和 TCA 组 (1.421 ± 0.076; P=0.001) 的血管弯曲度较高。血管病组 (1.324 ± 0.038; P=0.098)，脑梗死组 (1.348 ± 0.052; P=0.089)，心源性栓塞组 (1.379 ± 0.066; P=0.190) 的弯曲度与对照组并无差异。尽管自发性夹层组的血管弯曲度变异更高 (P=0.018)，但是创伤性夹层组 (1.391 ± 0.036) 和自发性夹层组 (1.403 ± 0.090; P=0.671) 血管弯曲度的平均值没有统计学差异。

讨论

研究结果表明，在儿童卒中中，不同动脉疾病的动脉迂曲程度不同，尤其是夹层和 TCA。儿童的动脉迂曲度似乎可以通过 MRA 精确地测量。动脉迂曲度可能是一个可以理解儿童卒中病理生理学的反映血管生物学的影像标志物。

动脉先天形成和在各个年龄段的特异性脑血管疾病中起着作用。遗传性结缔组织病导致的脑动脉病的人数在持续增长，如胶原 4A1 和 A2、马耶夫斯基成小头畸形脑发育不良原始侏儒症 II 型、平滑肌肌动蛋白 (ACTA2) 等。这些疾病常常早期发病，伴有整个动脉主干及其他器官可能存在的并发症。夹层引起的成人卒中，结缔组织病已得到广泛证实，包括大部分伴有胶原蛋白或弹性蛋白病变而无症状的患者，或在电子显微镜下可见的其他皮肤结缔组织病。最近的一个成人卒中研究描述了目测动脉迂曲度和夹层之间关系。将病理学的发现和遗传学的发现联系在一起可以更容易辨认影像学生物标志，如动脉迂曲，早期认识这种机制可以更好地管理儿童卒中。

TCA 是早已得到认可的影像综合征，但其病理生理学机制仍然是儿童卒中最复杂和最具争议的问题之一。尽管我们应用最好的一致性影像标准分类，TCA 的临床影像学特征仍和其他形式的 FCA 不同。有限的和无远期感染相关的流行病学研究，以及缺乏炎症相关的实验或影像学标志物，对原发性感染或炎症这样机制的合理性提出了质疑。该研究发现在 TCA 的儿童中平均动脉迂曲度不同，这促使学者对 TCA 新的生物学机制的思考。脑动脉先天的特征被预设定为获得性感染或炎症过程的一个特殊部分似乎是不合理的。

颅内动脉夹层是引起 TCA 的主要原因么？尽管有许多有趣的、合理的理论支持炎症，可能的类感染是 TCA 的发病机制，但仍缺乏确凿的证据。在一个小病例系列的研究中，与心源性栓塞性卒中儿童相比，患有 TCA 的儿童致炎性生物标志物出现短暂的异常。另一个小病例研究描述了 3 例死亡的 TCA/FCA 儿童，尸检提示有颅内动脉夹层的病理学证据，但无炎症的证据。同样值得注意的是，这两种可能并不相互排斥（如，急性炎症引起的动脉损害可能更易发生夹层性的病损）。

图 3 各对动脉弯曲度。箱型图内每点代表各血管测量的弯曲度，成对的弯曲度是均对的。其中颈内动脉弯曲度最大，基底动脉弯曲度最小。注：ICA：颈内动脉；L：左侧；M1：大脑中动脉第一段；R：右侧。
图5 不同疾病的动脉曲度。对照组(左侧箱型图，n=15)描述了儿童动脉曲度的正常范围，阴影部分为对照组5%和95%百分位点。夹层(n=22)和短暂性大脑动脉病变(n=25)组的曲度反常增高，其曲度方差也增高。外伤性(n=9)和自发性(n=13)夹层组间无差异。注：Moyamoya：烟雾病；TCA：短暂性大脑动脉病变。

该研究发现，TCA和动脉夹层性病变对脑局部或较远位置的动脉迂曲的增加程度相当。这一病理学发现将他们从正常对照和其他儿童动脉缺血性卒中亚型患者中区分出来，但并不能证明TCA就是颅内动脉夹层。这的确引起了更深入的思考，动脉的先天结构本身可能是疾病潜在发病机制的重要组成部分。

该技术提供了一种可以直接客观量化血管结构异常的方法。然而，存在一些方法学上的问题。因为这是一个运用了不同MRI设备的多中心研究，并非所有的影像资料被标化。某些影像学数据存在无法使用或者不完整的问题。这个软件技术也可以通过计算血管中心线的方式得以优化。三维时间飞跃法MRA原始图像包括一些来自于骨骼的体像素信息，在某些情况下这会干扰中心线的计算，无法分析来自于大脑前脑动脉较弱的影像学信号。增加可用的计算功率和改进算法可能会提升我们捕捉小血管结构的能力。在该研究中，迂曲分值为每个主要血管的迂曲分值的平均值。然而，动脉病变对动脉产生的影响是特异的。

结论
动脉迂曲程度在儿童卒中中是可以量化的，其可作为血管生物学中一种临床相关的影像学标志物。伴(颅内)动脉夹层的儿童动脉迂曲程度增加，在外伤性与自发性夹层之间未发现显著性差异。动脉迂曲是否可以反映动脉结构的先天性畸形仍需进一步探讨。患有TCA综合征的儿童其动脉迂曲程度有增加趋势，这也间接证明了先前关于某些TCA病例属于颅内夹层的设想。

参考文献