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; Jacqui Hodge, MSc; Adam Kirton, MD, MSc; and the Vascular Effects of Infection in Pediatric Stroke (VIPS) Investigators*

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
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 serum samples (and cerebrospinal fluid, when clinically obtained), standardized brain and cerebrovascular imaging. Importantly, all imaging was reviewed and classified by both the site investigator and standardized visual categorization of cervical arterial tortuosity found an association with extracranial dissection. 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 final voxel 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.

#### 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 study of top 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 Euclidian (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 final voxel 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
The primary hypothesis was tested using an 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 a \( \alpha = 0.05 \), 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; \( P=0.001 \)) 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

### 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>9.5±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.
Stroke May 2016

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.17 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.18 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.4 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), Amlie-Lefond C (Seattle Children’s Hospital, WA), Diamini 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).

Sources of Funding

The Vascular Effects of Infection in Pediatric Stroke (VIIPS) study (R01 NS062820) was funded by National Institutes of Health. F. Wei was funded by Alberta Innovates–Health Solutions. A. Kirton was funded by Alberta Innovates–Health Solutions and Heart and Stroke Foundation of Canada. The other authors report no conflicts.

Disclosures

None.

References


Arterial Tortuosity: An Imaging Biomarker of Childhood Stroke Pathogenesis?
Felix Wei, Karl T. Diedrich, Heather J. Fullerton, Gabrielle deVeber, Max Wintermark, Jacquie Hodge, Adam Kirton and the Vascular Effects of Infection in Pediatric Stroke (VIPS) Investigators

Stroke. 2016;47:1265-1270; originally published online March 22, 2016; doi: 10.1161/STROKEAHA.115.011331

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/5/1265

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2017/07/10/STROKEAHA.115.011331.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
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，颅外动脉类以与结缔组织病关系密切。尽管动脉性脑动脉病的病理生理学尚不明确，但是可能的原因也包括颅内动脉类以及短暂性脑动脉病等。本研究通过分析儿童卒中患者中的动脉迂曲进行量化分析，验证动脉夹层疾病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月至18岁的伴有缺血性卒中的儿童，对照组来自卡尔加里儿童卒中项目。多名研究者对诊断标准进行制定。使用通过验证的影像软件计算通过三维时间飞跃法磁共振血管成像序列呈像的颅内大血管的平均动脉迂曲度。比较动脉夹层、短暂性脑动脉病、颅内动脉炎、颅内血管类及心源性卒中的儿童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类及自发的动脉类的动脉迂曲度（t检验）。

结果: 研究共纳入115例儿童，其中43%为女性。实验组和对照组的年龄和性别项匹配。动脉夹层的均值和方差与验证研究一致。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）、颅内动脉炎（1.348±0.052；n=11；P=0.989）及心源性卒中（1.379±0.056；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±0.048；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: 动脉迂曲可能是一个连接先天血管结构和血管生物学的窗口。动脉迂曲增加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

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，颅外动脉类以与结缔组织病关系密切。尽管动脉性脑动脉病的病理生理学尚不明确，但是可能的原因也包括颅内动脉类以及短暂性脑动脉病等。本研究通过分析儿童卒中患者中的动脉迂曲进行量化分析，验证动脉夹层疾病中动脉迂曲的比例增加。

研究人群: 这是一个儿童卒中感染对血管影响（Vascular Effects of Infection in the Pediatric Stroke，VIPS）研究的亚组分析。研究的详细方法学在之前的研究中已经详细描述。VIPS是关于儿童动脉缺血性卒中的前瞻性多中心研究。VIPS研究招募年龄在1月至18岁的由磁共振血管造影证实存在急性缺血性卒中的患儿。对那些卒中患者进行沟通，该研究采集血样和血清标本（包括脑脊液），收集完善的影像学资料。研究中所有影像学数据由两个研究小组和额外的统一的多个专家进行盲法评审。首先，每一份病例由中央审查委员会用规范化的标准，将其分为以下三类:诊断明确的、诊断可能的或者没有动脉病变的。其次，对那些有动脉病变的进一步归类为二
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，将所有纳入患者的大脑动脉影像以 DICOM 格式，从三维时间飞跃法 MRA 获得。该研究应用高质量的影像学诊断标准。像 TCA 和夹层这类疾病中的病变节段被排除在外。通过对三维空间中的每个二维层图像的算法迭代，计算每根动脉管腔的横截面和其他原位区域的质点 (单像素)，这些中心点连接以形成中心线构成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，这个值叫做距离因素指标 (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移动选择 2 个端点。由于颈内动脉和椎动脉在颈部下行，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。如椎动脉的汇合点或 Willis 环内动脉的分岔点。第 2 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 值的动脉的，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 图 2。MRA 造影曲度测量。示例通过弯曲范围计算。原始中 TOF MRA 图像中 MIP (top) 以及重建冠状面上相应点 (bottom) 可以表示出最低值 (1.237)、平均值 (1.460) 和最高值 (1.608)，这就是曲度评分的范围。 注: MRA: 磁共振血管造影；TOF: 时间飞跃法；MIP: 最大信号投影；mDFM: 最大距离测量标准值。
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的血管迂曲度采用 t 检验分析。使用方差分析（post hoc Tukey 法）分析所有配对血管。使用方差分析（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的血管迂曲度采用 t 检验（平均值）和方差齐性检验（方差）方法分析。评估者间的单盲分析得出，评估者间对迂曲度的平均值和方差性评估方面有高度可重复性（所有组内相关性 > 0.95）。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。各组之间的弯曲度评分均符合正态分布。对照组（93% 的图像为头颅患者）弯曲度评分的平均值为 1.333（中位值，1.331），得分为 1.283 与 1.443 之间。平均值、范围和差异与之前公布的数据一致。

该研究中，不同动脉血管间的弯曲度曲线存在差异（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，这与左侧解剖特点的不同是相一致的。左右半球动脉的血管弯曲度得分特点是相同的（如左鼓室内动脉 M1 段与右鼓室内动脉 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）。弯曲度的变异系数为 0.039。在控制测量误差的基础上，弯曲度 5% 百分位点和 95% 百分位点分别为 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。其中颈内动脉 M1 段病变（1.324 ± 0.038; P=0.998），脑干动脉（1.348 ± 0.062; P=0.898），脑干动脉 M1 段（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，不同动脉疾病的血管迂曲程度不同，尤其是夹层和 TCA。儿童的动脉迂曲度依靠 MRA 精确地测量。动脉迂曲度可能是可以帮助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。

动脉先天结构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、马耶夫斯基或小头畸形骨发育不良原始侏儒症 2 型、平滑肌肌动蛋白（ACTA2）等。这些疾病通常有家族病史，伴有多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异常的无症状的患者，或在电子显微镜下可见的其他皮肤结缔组织异常。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的关系。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标志，如动脉迂曲，早期认识到这种机制可以更好地管理儿童卒中。

TCA 是已有的研究标志，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和有力的影像标准分类，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。颅内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，但仍缺乏确切的证据。在一个小病例系列的研究中，与无显性症状性卒中儿童相比，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在夹层性的病损）。
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特征。伴随（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 病例源于颅内夹层的设想。

参考文献