Original Article

Basilar Artery Angulation in Association with Aging and Pontine Lacunar Infarction: A Multicenter Observational Study

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Aim: Deep pontine lacunar infarction (DPLI) not involving the basal pial surface of the medial part of the pons, is known to be a small vessel disease in the territory of the basilar artery (BA). In the present study, we examined whether morphological features of the BA differ in individuals with an advanced age and may be associated with DPLI.
Methods: This study included 338 healthy subjects and 78 patients with DPLI treated at the stroke centers of three university hospitals in Korea. Time-Of-Flight magnetic resonance angiographic images were transported to a central lab and analyzed blind to obtain the clinical data. For the quantitative analysis, the BA was projected two-dimensionally in the anteroposterior and lateral views and perceived as triangles of the vertebrobasilar junction, angulation point and BA division. The angles and triangular areas were summated into angulation indexes and used to quantify the degree of BA tortuosity.
Results: The BA showed a more acute angle at the angulation point in the elderly patients than in the healthy subjects. Compared to the healthy subjects, the DPLI patients exhibited significantly larger angles at the vertebrobasilar junction, in addition to the acute angles noted at the angulation point. A unit increase in the BA angle indexes at the vertebrobasilar junction and angulation points for DPLI was found to have an odds ratio of 1.15 (95% confidence interval, 1.05-1.26) and 0.95 (95% CI, 0.91-0.99), respectively, even after adjusting for potential confounders.
Conclusions: The angulation point of the BA becomes more acute in elderly individuals. In this study, the vertebrobasilar junction showed a larger angle in the patients with DPLI than in the healthy controls.

J Atheroscler Thromb, 2015; 22: 509-517.

Key words: Aging, Angulation, Basilar Artery, Deep Pontine Lacunar Infarction

Introduction

The basilar artery (BA) is one of the largest cerebral arteries and known to be affected most commonly by atherosclerosis, particularly in the mid to distal portions[1]. A unique feature of the BA is that it displays angulation in its course due to its anatomic relationships with surrounding structures, with two components of BA angulation to be analyzed, as we reported previously[2].

The BA lodges anterior to the brainstem, receiving blood from the vertebral arteries and supplying blood to the posterior cerebral arteries. Both the vertebral arteries and posterior cerebral arteries are located posterior to the brainstem. The BA naturally exhibits angulation along its course, and the angulation point may be affected by the shear force of the blood flow originating from the vertebral arteries. Therefore, the angulation point may become deformed in advanced age due to the effects of a continuous blood flow.

The BA supplies blood in an anterior to posterior direction. Changes in the geometry of the BA with age may have an effect on the pontine blood supply, especially in the deep pontine region. In the middle pontine tegmentum, there is no collateral blood supply from either the lateral to medial or posterior aspects of the pons. Deep pontine lacunar infarction (DPLI) typically occurs in this area, involving the medial part of the pons but not the basal pial surface[3]. DPLI is known to be caused by small vessel lipohyalinosis[4], although further research is required to clarify the pathophysiology of this condition.

In the present study, we aimed to examine 1) whether the morphology of the BA changes with age, and 2) which morphological features of the BA are potentially associated with DPLI. For this purpose, we invented a new method to quantify the degree of BA angulation and subsequently applied this method in healthy subjects in order to identify age-associated morphological changes in the BA and compared various BA angulation indexes between patients with DPLI and control subjects.

Subjects and Methods

Study Population

This study included data for two groups: 1. healthy subjects 20 to 79 years of age who underwent brain magnetic resonance imaging (MRI) and Time-of-Flight (TOF) MR angiography between March 2008 and February 2010 for health screening at Chonbuk National University Hospital, and 2. patients with DPLI enrolled from three university hospitals in the Honam area, South Korea (Chonbuk National University Hospital, Jeonju City; Chonnam National University Hospital, Gwangju City; and Wonkwang University Hospital, Iksan City) during the same time period. DPLI was defined as a history of pontine infarction in the medial part of the pons not involving the basal pial surface with evidence of acute focal neurological dysfunction and symptoms lasting more than 24 hours. Such symptoms were thought to be due to pontine ischemia, as confirmed on brain MRI, with high signal intensity on diffusion-weighted imaging (DWI) and low signal intensity on the apparent diffusion coefficient map. The DWI images were examined within one day after the onset of symptoms. This study was conducted with the approval of the institutional ethics committees of the three university hospitals.

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Received: May 21, 2014
Accepted for publication: September 25, 2014

Inclusion/Exclusion Criteria

Patients diagnosed with DPLI on brain diffusion-weighted MR images and TOF MR angiography were included in this study. The diagnosis of DPLI was originally made by three stroke specialists (Y.S.H., J.T.K. and S.K.J.) in their respected hospitals, and all images were interpreted interchangeably, with a final agreement reached before enrollment. Patients with lateral pontine or paramedian pontine infarction involving the basal pial surface were excluded. Healthy subjects who underwent brain MRI and TOF MR angiography during the health screening examinations were included and enrolled in the control group. Individuals with evidence of ischemia on brain MRI (among the healthy subjects) or abnormal hepatic, renal or hematological laboratory findings were excluded.

Assessments and Measurements

The data in the present study were collected retrospectively and included the following variables: history of cardiovascular disease, type 2 diabetes mellitus (DM), hypertension and dyslipidemia, smoking status and medications. The smoking status was classified into three categories: current smoker, ex-smoker and non-smoker. Patients exhibiting persistent elevation of blood pressure (i.e., ≥140/90 mmHg) or those receiving antihypertensive medications were classified as being hypertensive[5]. Subjects were classified as having type 2 DM if they stated that a physician had told them they had diabetes or if their fasting blood glucose level was above 7.0 mmol/L on more than two occasions[6]. Hyperlipidemia was defined as a total cholesterol level greater than 6.2 mmol/L or LDL cholesterol level greater than 4.1 mmol/L[7]. Blood samples for the analysis were drawn in the morning after a 12-hour overnight fast.

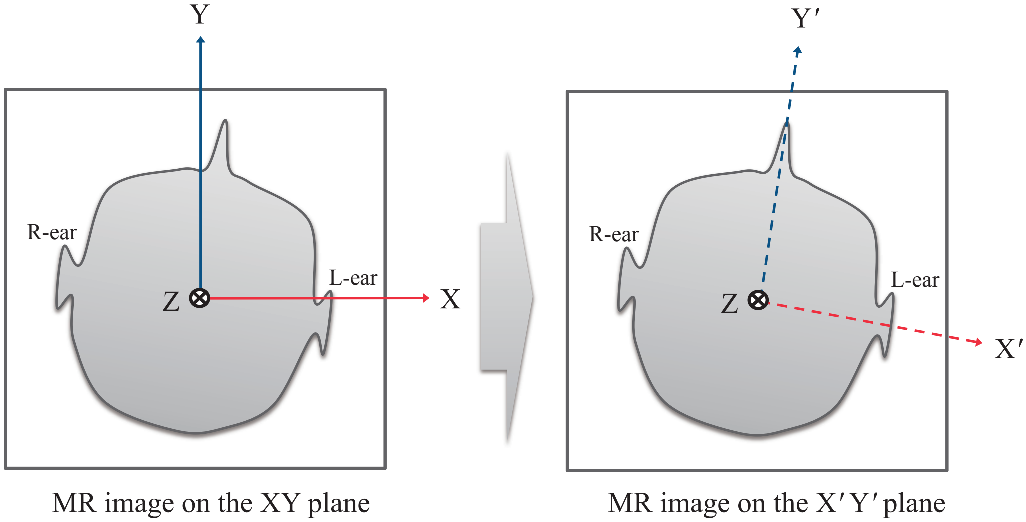

Fig. 1. Anteroposterior (AP) calibration for correction of the head position on the layered TOF MR angiographic images. A) An MR image in the XY plane (before correction). B) An MR image in the X'Y' plane (after correction).

TOF MR Angiography

All patients and healthy subjects underwent brain MRI and TOF MR angiography at one of the three university hospitals. The imaging parameters for the 3D TOF MR angiographic scans were as follows: repetition time (TR)/echo time (TE) = 23-25/3.45 ms; flip angle = 20°; field of view (FOV) = 200 × 200 mm; matrix size = 488 × 249; sensitivity encoding (SENSE) factor = 2; slice thickness = 0.50 mm; and number of average (NEX) = 1. The TOF-MR angiography scan time was approximately 5.46 minutes. The imaging parameters for DWI were as follows: TR/TE = 3,000/80 ms; flip angle = 90°; FOV 220 × 220; matrix size = 128 × 128; slice thickness = 5 mm; and NEX = 2. The diffusion-weighted image scan time was approximately 1.40 minutes. All brain MRI and TOF MR angiography images were transported to a central lab at Chonbuk National University Hospital for detailed image analyses.

Geometric Measurement of the BA with 2D Projected Images

The geometric characteristics of the vertebrobasilar artery and degree of intracranial arterial stenosis on TOF MR angiography were defined and interpreted by two neurologists (J.H.L. and S.K.J.) and projected by certified neuroradiologists (G.H.C. and H.S.K.). The geometric characteristics of the vertebrobasilar artery included vertebral artery dominance and BA curvature (right or left deviated). Cerebral arterial stenosis was defined as more than 50% stenosis in the distal (V4) portion of the vertebral arteries, BA and posterior and middle cerebral arteries using source images and 3D reconstructed views of TOF MR angiography[8].

We developed the BA angulation indexes using the algorithms described below. In order to identify and analyze hemodynamic information for the BA, we simplified the BA as triangles with two references (the vertebrobasilar junction and the division of the BA) and angulation points. Axial source images of the vertebrobasilar artery were obtained via TOF MR angiography and used to reconstruct multiplanar sections in the same screen, including the XZ (coronal) and YZ (sagittal) planes, with our own in-house code, as previously described[2]. Using the multiplanar sections, the two references and the most angulated points were selected and designated as three-dimensional (3D) Cartesian coordinates. The images and 3D coordinates were then projected two-dimensionally (2D) to the lateral and anteroposterior (AP) views.

Algorithms for the BA Angulation Indexes

AP Calibration

For correction of the head position on the layered MR images in the XY plane, the images were calibrated (or modified) onto the modified X'Y' plane (**Fig. 1**). In the X'Y' plane, the X' axis was set to be in line with both ears, and the Y' axis with the nose.

Selection of Reference Points

In order to generalize individual variation in BA

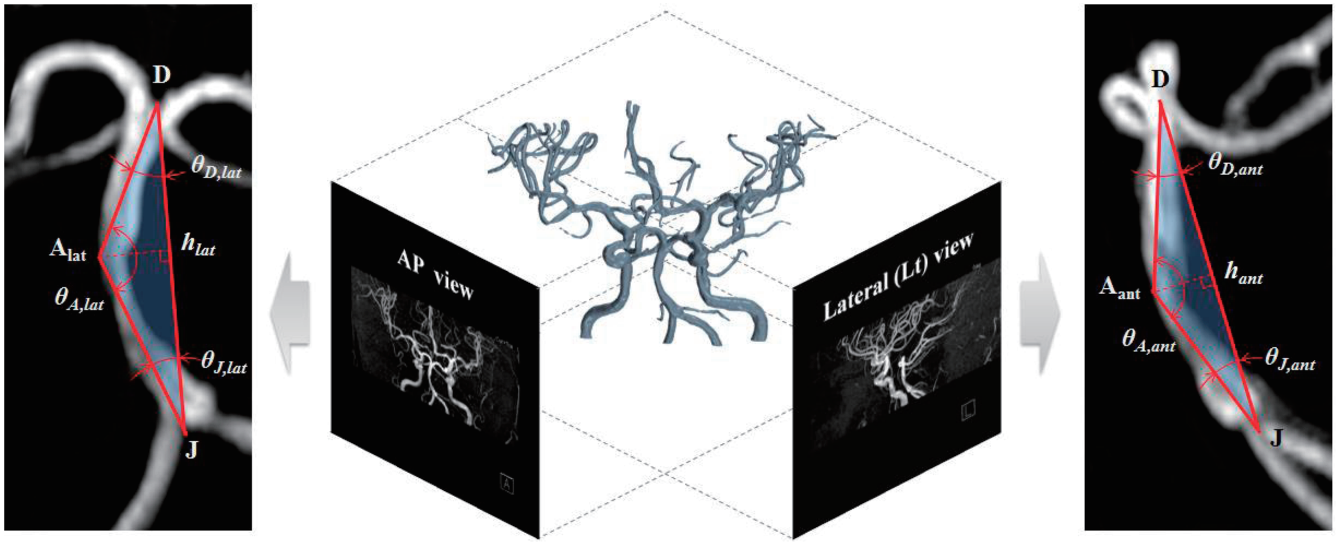

Fig. 2. A schematic presentation of the angulation indexes of the basilar artery (BA). Lateral angulation of the BA was observed from the AP view (left), and anterior angulation of the BA was observed from the lateral view (right). J is the point of the vertebrobasilar (VB) junction, D is the point of the BA division and A_{lat} and A_{ant} are the most angulated points laterally and anteriorly, respectively. Using 2D projected images on the XZ or YZ planes, the BA angulation indexes were calculated as follows: angle indexes $=(\theta_{ant}^2+\theta_{lat}^2)^{1/2}$ for angles J, A and D, triangular area index $=(a_{ant}^2+a_{lat}^2)^{1/2}$ and triangular height index $=(h_{ant}^2+h_{lat}^2)^{1/2}$. The subscript *ant* represents the degree of anterior angulation from the lateral view, while *lat* represents the degree of lateral angulation from the AP view. All values for anterior and lateral angulation were weighted evenly with a factor of 0.5.

geometry, the reference points for the vertebrobasilar junction [J] and the division point of the BA [D] were selected from the source images using the multiplanar sections simultaneously.

Search for Angulation Points

In order to evaluate the tortuosity of the BA, we searched for both lateral angulation (A) points along the BA in the XZ (coronal) plane and anterior angulation points along the YZ (sagittal) plane. In the two planes, the angulation points (A_{lat} or A_{ant}) were obtained to maximize the triangular area (Δ JAD).

Measurement of the Triangular Angles, Area and Height

The references (J, D) and angulation points (A) were then projected two-dimensionally onto the X'Z (AP view for lateral angulation) and Y'Z (lateral view for anterior angulation) planes (**Fig. 2**). Three triangular angles (J, A and D), and triangular areas and heights were then measured.

If the angle is clockwise with respect to the reference plane, the angle has a positive sign, and vice versa. Therefore, the range of the angle is between −180° and 180°.

Calculation of the BA Angulation Indexes

The BA angulation indexes for the three angles (J, A and D) and the triangular areas and heights obtained from the two projected images were calculated as follows:

Angle indexes $=(\theta_{ant}^2+\theta_{lat}^2)^{1/2}$ for angles J, A and D, respectively
Triangular area index $=(a_{ant}^2+a_{lat}^2)^{1/2}$
Triangular height index $=(h_{ant}^2+h_{lat}^2)^{1/2}$

where θ represents the angle, a represents the triangular area (Δ JAD) and h represents the height of the triangle. The subscript *ant* represents the degree of anterior angulation from the lateral view (Y'Z plane) and *lat* represents the degree of lateral angulation from the AP view (X'Z plane). All values for anterior and lateral angulation were weighted evenly with a factor of 0.5.

Statistical Analysis

Descriptive data are expressed as the mean ± standard deviation (SD) or percentages, as appropriate. The independent t-test was used to analyze continuous variables and the chi-square test was used to analyze categorical variables. Sex-adjusted correlations were evaluated to assess the relationships between the

Table 1. Demographics

	DPLI	Control	p
Number	78	338	
Age, yrs	64.4 ± 10.5	56.5 ± 9.8	< 0.001
Women, %	44.9	44.0	0.883
Smoker, ex- or current, %	32.1	23.6	0.121
Alcohol drinking, current, %	38.5	46.6	0.192
Hypertension, %	67.9	28.0	< 0.001
Type 2 diabetes, %	30.8	14.5	0.001
Hyperlipidemia, %	35.9	28.0	0.169
Hematocrit, %	40.6 ± 4.3	42.6 ± 4.2	0.011
Serum creatinine, mmol/L	80.2 ± 82.3	67.1 ± 16.2	0.148
Patients from each center, %			
CBNU	50.0		
CNU	33.3		
WU	16.7		

The values are presented as the mean ± standard deviation or percentage, as appropriate.
DPLI, deep pontine lacunar infarction; CBNU, Chonbuk National University; CNU, Chonnam National University; WU, Wonkwang University
The p values are from the independent t-test or chi-square test, as appropriate.

BA angulation indexes and age. A multivariate logistic regression analysis was used to determine the associations between DPLI and the BA angulation indexes, with the results presented as the odds ratio (OR) and 95% confidence interval (CI). In the multivariate analysis, all possible confounders exhibiting significance ($p < 0.1$) were adjusted. We also assessed inter-individual stability and intra-individual test-retest reliability in 30 subjects. All statistical analyses were performed using the SPSS software program version 16.0 (SPSS, Chicago, IL, USA).

Results

In total, 338 healthy subjects and 78 patients with DPLI were enrolled and evaluated in the present study. Approximately 32 subjects (8.6%) and 18 patients (18.8%) were excluded due to the presence of a unilateral vertebral artery or having inappropriate scans of the distal portion (V4) of the vertebral arteries. The DPLI patients were enrolled from Chonbuk National University Hospital ($n=39$), Chonnam National University Hospital ($n=26$) and Wonkwang University Hospital ($n=13$), respectively, as shown in **Table 1**. The DPLI patients were older and had greater rates of hypertension and type 2 diabetes and lower hematocrit levels.

The BA was mostly deviated to the anterior direction and more likely to be deviated to the right lateral direction in both groups, as shown in **Table 2**. The MRA scans were obtained with the participant's head slightly rotated counterclockwise (right deviated) in more cases. The DPLI patients showed significantly higher angle indexes at the vertebrobasilar junction with lower angle indexes at the angulation point and exhibited significantly higher frequencies of unilateral dominance of the vertebral artery and intracranial atherosclerotic stenosis.

In the healthy subjects, the distances between the vertebrobasilar junction and the division points increased significantly with advancing age, as shown in **Table 3**. Among the BA angulation indexes, the angle index at the angulation point demonstrated a significantly decreasing trend with age, while both the triangular area index and height index showed increasing trends. The BA angle index at the vertebrobasilar junction did not display any significant changes with age. The correlations between the BA angulation indexes and age lost significance after adjusting for vascular risk factors (data not shown).

The angle indexes at the vertebrobasilar junction were significantly and independently associated with DPLI, with an OR of 1.15 (95% CI, 1.05-1.26, per unit), even after adjusting for potential confounders, as shown in **Table 4**. The angle indexes at the angulation point were also significantly but negatively associated with DPLI, with an OR of 0.95 (95% CI, 0.91-0.99). The inter-individual correlation coefficients for the BA angulation indexes in the 30 subjects ranged from 0.75 to 0.86, while the intra-individual correla-

Table 2. Morphological characteristics of the basilar artery (BA)

	DPLI	Control	
Antero-posterior angle calibration, °	− 3.5 ± 3.2	− 4.8 ± 2.7	0.708
BA, anterior angulated, %	97.4	98.5	0.500
BA, right lateral angulated, %	56.4	66.1	0.108
BA, Junction to Division, mm	27.4 ± 4.4	27.1 ± 5.0	0.727
BA angulation indexes			
Angle index, VB junction, °	19.3 ± 7.1	16.4 ± 4.5	0.047
Angle index, angulation point, °	95.9 ± 8.2	98.2 ± 6.8	0.009
Angle index, division point, °	14.6 ± 4.8	14.2 ± 4.2	0.646
Triangular area index, mm^2	48.8 ± 20.6	49.1 ± 22.1	0.898
Triangular height index, mm	3.7 ± 1.2	3.6 ± 1.1	0.429
Vertebral artery dominance			< 0.001
No dominance, %	37.2	90.3	
Right dominance, %	20.5	5.0	
Left dominance, %	42.3	4.7	
Vertebral artery (V4 portion) stenosis*, %	17.9	0.9	< 0.001
BA stenosis, %	9.0	0.6	< 0.001
PCA stenosis, %	19.2	2.7	< 0.001
MCA stenosis, %	19.2	9.7	0.018

*Arterial stenosis was defined as greater than 50% luminal narrowing
VB, vertebrobasilar; BA, basilar artery; PCA, posterior cerebral artery; MCA, middle cerebral artery

tion coefficients for the indexes at 14-day intervals ranged from 0.71 to 0.85.

Discussion

The present study identified morphological changes in the BA that occur with age, manifesting as greater acute angles of the angulation point in elderly patients. Among the morphological features of the BA, a larger angle at the vertebrobasilar junction was found to be independently associated with DPLI, even after adjusting for potential confounders, including vascular risk factors. The geometry of the BA has been measured previously using angiographic images[9]. We modified this method in order to improve our quantitative analysis using 3D Cartesian coordinates and 2D projection images.

It is reasonable that the BA changes into a more angulated form with age due to its unique anatomic relationships. The BA receives blood from the vertebral arteries and supplies blood backward (to the posterior cerebral arteries). The BA may be angulated anteriorly (from the lateral view) and laterally (from the anteroposterior view) due to the effects of blood inflowing from the vertebral arteries. Inflowing blood originating from the vertebral arteries exerts a centrifugal force around the angulation point. The force along the proximal portion of the BA pushes the angulation point upward (distally) and changes the geometry of the BA with advancing age, as thoroughly documented in **Table 3**. In addition to aging, vascular risk factors have variable effects on these arterial remodeling processes[10]. Subsequent studies are needed to clarify the effect of each vascular risk factor on BA remodeling.

Interestingly, the DPLI patients in this study showed larger angles at the vertebrobasilar junction, and this association remained independent, even after adjusting for potential confounders. The angle of the vertebrobasilar junction may be a determinant of secondary geometric changes in the BA based on the direction of the blood flow. If the angle of the vertebrobasilar junction is large, the force of the blood flow will more effectively cause the angulation point to exhibit a more acute angle in advanced age. In contrast, the angle indexes of the vertebrobasilar junction did not show any significant changes with age in the healthy subjects in this study, as shown in **Table 3**. These findings suggest that the angle index at the vertebrobasilar junction is larger in DPLI patients than in controls, irrespective of aging.

The determinants of the angle index at the vertebrobasilar junction include 1) the degree of side-to-side variation in the size of the vertebral arteries and 2) the measurements of the confluent angles from the vertebral arteries to the BA. The degree of side-to-side

Table 3. Sex-adjusted associations between the angulation indexes of the BA and age in the healthy subjects

	Sex-adjusted mean values of BA angulation indexes according to age, yrs					*p*, between groups	*p*, linear trend
	20-39	40-49	50-59	60-69	70-79		
VB Junction to BA Division, mm	25.6±1.2	26.4±0.5	27.0±0.4	28.7±0.5	27.5±0.7	0.004	0.003
BA angulation indexes							
Angle index, VB junction, °	13.2±1.2	16.5±0.6	16.5±0.4	16.6±0.5	16.6±0.7	0.154	0.222
Angle index, angulation point, °	103.5±1.9	98.5±0.8	98.2±0.6	97.7±0.7	97.1±1.1	0.048	0.024
Angle index, division point, °	12.3±1.2	14.0±0.5	14.3±0.4	14.2±0.4	14.7±0.4	0.477	0.188
Triangular area index, mm^2	35.9±6.1	46.8±2.7	48.3±1.9	53.1±2.3	50.9±3.6	0.069	0.016
Triangular height index, mm	2.8±0.3	3.5±0.1	3.6±0.1	3.7±0.1	3.7±0.2	0.143	0.045

Table 4. Multivariate associations between the BA angulation indexes and DPLI

	DPLI		*p*
	Odds ratio	95% confidence intervals	
BA angulation indexes			
Angle index, VB junction, °	1.15	1.05-1.26	0.003
Angle index, angulation point, °	0.95	0.91-0.99	0.026
Angle index, division point, °	1.02	0.92-1.13	0.744
Triangular area index, mm^2	1.00	0.99-1.02	0.809
Triangular height index, mm	1.18	0.89-1.56	0.244

The analysis was adjusted for age, sex, hypertension, type 2 diabetes, hematocrit, VA, BA, PCA and MCA atherosclerosis and VA dominance.

variation in the size of the vertebral arteries may affect the extent of lateral angulation, while the differences in the confluent angles from the vertebral arteries to the BA may influence the amount of anterior angulation. The diameters of the right and left vertebral arteries are variable, being equal in only 6-26% of patients, according to angiographic and postmortem studies[11]. The patients with DPLI in the present study also showed a significantly higher percentage of unilateral dominance. The vertebral artery is reported to be significantly associated with the size of the transverse foramina[12] and its tortuosity is associated with adverse outcomes in young patients with connective tissue disorders[13]. However, there have been no previous studies regarding the differences in the confluent angles between the terminal portion of the vertebral artery and the proximal portion of the BA. More studies are thus needed to examine whether the angle index at the vertebrobasilar junction has predictive power for DPLI as well as other forms of brainstem infarction.

The lower (or more acute) angle indexes at the BA angulation point observed in the DPLI patients in the present study suggest that these patients had a more tortuous arterial geometry than the controls. Because the indexes were calculated based on anterior and lateral projected images of the BA, lower index values indicate that the BA bended more anteriorly and laterally from the reference line from the VB junction to BA division, where the pons is located. The paramedian perforating artery supplies the paramedian pontine tegmentum, and there is no collateral blood flow; therefore, the blood flow to the pontine tegmentum likely travels a longer distance from the parent BA in patients with lower BA angulation indexes. The long and tortuous penetrating arteries from the parent BA may cause tissue hypoxia more easily[14, 15].

The morphological features of the vertebrobasilar artery have been previously reported to have hemodynamic effects on brainstem infarction[16-18]. The hemodynamics of the BA are more effectively interpreted based on the two components of angulation, as these features determine the flow dynamics and rate of atherosclerotic progression[2]. In the present study, most of the subjects showed anterior angulation of the BA on the lateral view (**Table 1**), such that the regions experiencing low wall shear stress along the lesser curvature may be shifted to the posterior side of the BA (near the brainstem). In patients with lower angle indexes at the BA angulation points, the region of low wall shear stress is easily focused on the posterolateral side of the BA, thus inducing atherosclerosis more efficiently. Low wall shear stress is known to cause blood to stagnate, subsequently interacting with the vessel wall[19] and ultimately causing atherosclerotic progression[20]. Even with slight impingement of the arterial orifice due to atherosclerosis[21, 22], the blood flow is correspondingly reduced to the fourth power of the diameter of the artery, in accordance with Poiseuille's law[23]. A reduced blood flow through the perforating arteries may cause tissue damage to both the arterial wall and pontine tegmentum, as reported previously in an autopsy study[4] and high-resolution MRI study[24]. Therefore, subjects with lower (or more acute) BA angulation indexes will have a longer distance from the BA to the pontine tegmentum with a consequent adverse hemodynamic environment of lower shear stress in the BA.

In the present study, the geometric characteristics of the BA were measured using a newly developed BA angulation index, which employs two projected images. The anamorphic analysis involved the projection of 3D structures encoded as Cartesian coordinates (x, y, z) onto the X'Z (for lateral angulation) and Y'Z (for anterior angulation) planes. Hence, the present method is effective for measuring the degree of angulation of the BA quantitatively. Previous methods for analyzing BA geometry were largely dependent on 2D axial images (XY sections only)[25, 26] or maximum intensity projection (MIP) images[9, 16, 27]. However, the geometry of the BA cannot be measured appropriately using previous conventional methods for the following reasons: 1) the reference points frequently overlap and are obscured, and 2) the BA angles and distances are measured on randomly projected images, especially when using MIP images.

The present study is associated with some limitations. First, this was a retrospective case-control study; therefore, we could not determine the causal relationships between the BA angulation indexes and DPLI. However, multicenter studies using similar TOF MR angiographic settings may be helpful for reducing selection bias. Second, the sample size was smaller and the age distribution was older in the DPLI patients than in the controls. Although the sample size was not matched, the larger number of controls helped to identify age-associated changes in BA geometry. Finally, this study did not perform a flow dynamic analysis or examine the detailed intraluminal status of the BA using high-resolution MRI.

In conclusion, the BA shows gross anatomic changes with advancing age, including a more acute angle at the angulation point, possibly due to the effects of inflowing blood originating from the vertebral arteries. In this study, the DPLI patients exhibited significantly larger angles at the vertebrobasilar junction than the controls. Prospective studies are needed to examine potential associations between the angulation indexes and arterial hemodynamics and determine whether the present findings are repeatable in patients with other types of brainstem infarction in various populations.

Acknowledgements

This work was supported by the Research Institute of Clinical Medicine, Chonbuk National University and the Biomedical Research Institute of Chonbuk National University Hospital.

Author Contributions

J.H.L and D.H.N measured the BA angulation indexes and participated in drafting the manuscript. S.Y.O, G.H.C and H.S.K conceived the study design and reviewed the images and manuscript. J.T.K and Y.S.H conceived the study design and participated as subprincipal investigators. S.H.L and NH conceived the study design and reviewed the manuscript. S.H.P built the software program and reviewed the manuscript. S.K.J developed the software program, conceived the study and drafted the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interests

The authors have no conflicts of interest with regard to this study.

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