Relationship between the Angle of the Posterior Inferior Cerebellar Artery and Cardioembolic Stroke

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Background: In patients with unilateral posterior inferior cerebellar artery (PICA) territory infarction, the absence of relevant vessel stenosis may make it difficult to determine the etiology of the infarction. The incidence of cardioembolic (CE) infarction and the factors associated with infarction in such patients remains largely unknown. We hypothesized that the PICA angle would affect the flow direction of embolic sources. Thus, we analyzed the association between high-risk CE sources and the PICA angle. *Methods:* Patients with an isolated unilateral PICA territory infarction without relevant vessel stenosis who were admitted between 2014 and 2017 were included from the Korea University Stroke Registry, which includes data from 3 university hospitals. We classified patients according to the presence of CE sources. For each case, we measured the angle between the vertebral artery (VA) and the proximal PICA. *Results:* In all, 71 patients met the final study entry criteria. Multivariable analysis showed that the PICA angle was independently associated with the risk of a CE source. The optimal cut-off value using Youden's index was 89°. We classified the PICA shape based on the optimal cut-off value. A CE source was identified in 83.3% of cases in which the PICA angle exceeded 89°. *Conclusions:* The angle between the PICA and VA was an independent predictor of unilateral PICA stroke with high-risk CE sources without relevant artery stenosis, suggesting that an angle greater than 89° could be a new image marker for determining the stroke subtype.
Key Words: PICA infarction—PICA angle—Cardioembolism—PICA stroke

Introduction

Cerebellar infarction most commonly occurs in the posterior inferior cerebellar artery (PICA) territory.[1,2] The clinical features of PICA territory infarctions and the vascular anatomy of the PICA have been well defined.[3,4] However, the etiology of a PICA territory infarction may be difficult to identify because the vessel is too small to be visualized using computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Classically, the primary mechanisms of cerebellar infarction include distal embolization from cardiac or arterial sources and in situ arterial occlusion resulting from atherosclerosis.[5] Importantly, cardioembolic (CE) sources can cause multiple lesions in the cerebellar and associated vertebrobasilar territory.[2,6]

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In patients with subclavian, brachiocephalic, or vertebral artery (VA) stenosis, small territorial or nonterritorial PICA infarcts were presumably caused by an artery-to-artery embolism or low perfusion within the vertebrobasilar arteries where activation of thrombogenesis was the main risk factor.[7,8] If there are no stenotic lesions in the brachiocephalic, subclavian, or vertebral arteries in an infarction confined to the PICA territory, and if a lesion is limited to the PICA territory, it may be difficult to determine the etiology of such a stroke; possible causes include CE events or in situ atherothrombosis. In fact, it is difficult to distinguish the presence of atherosclerotic lesions in the PICA using MRA or CTA with relatively low resolution, because PICAs are generally small in diameter (approximately 2.2-2.5 mm).[9] Transfemoral cerebral angiography may be an alternative; however, this is an invasive procedure that is impractical to perform in all patients, and it may also be difficult to identify PICA lesions with this technique. We deliberated on the incidence of CE infarctions in the unilateral PICA territory without relevant vessel stenosis, and whether a CE source caused the infarction in these patients. We hypothesized that in patients with a CE source, the incidence of cerebral infarction may vary with the angle between the PICA and VA (acute versus obtuse) because the PICA angle would affect the flow direction of the embolic source. Thus, we analyzed the association between CE sources and the magnitude of the PICA angle.

Methods

Patients

A prospective multicenter database (Korea University Stroke Registry, which includes records from Ansan, Guro, and Anam Hospitals) was used to retrospectively screen consecutive patients diagnosed with ischemic stroke or transient ischemic attack within 7 days of symptom onset, between March 2014 and December 2017. The patients were included in the study based on the following criteria (Fig 1): (1) evidence of an acute ischemic lesion limited to the unilateral PICA territory on initial diffusion-weighted image; (2) magnetic resonance imaging (MRI)/MRA or CTA performed within 24 hours after admission; (3) no stenosis in the brachiocephalic, subclavian, and VA on MRA or CTA; (4) MRA or CTA not showing either dysplasia and/or hypoplasia in the VA; (5) all PICAs were enrolled only if they originated from the VA. VAs ending in the PICA were excluded. The study was approved by the ethics committees of the relevant institutions.

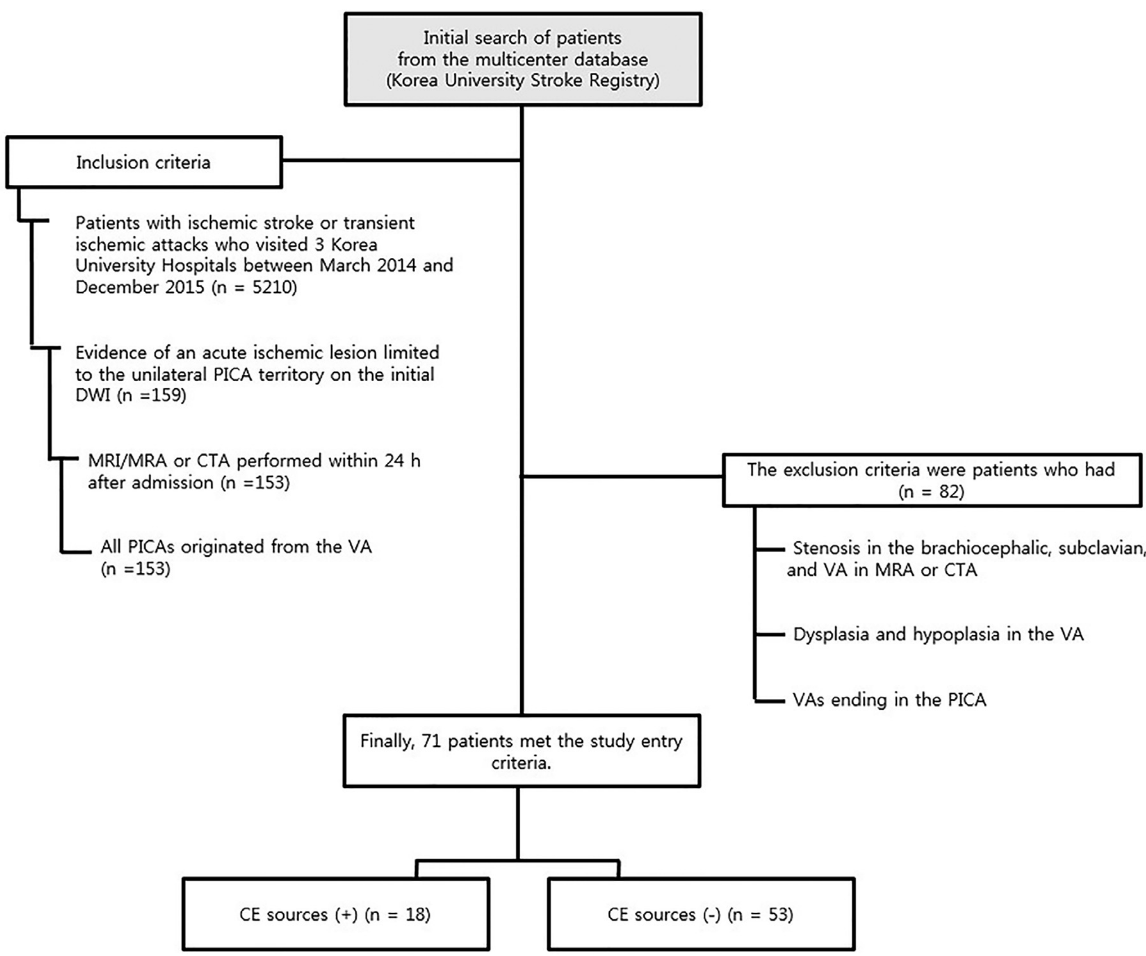

Figure 1. *Flowchart of the inclusion and exclusion criteria.*

Imaging Protocol

All patients underwent diffusion-weighted imaging, conventional MRI, such as T1-weighted imaging, T2-weighted imaging, and fluid-attenuated inversion recovery, and MRA, including time-of-flight of the circle of Willis and contrast-enhanced MRA of the circle of Willis and extracranial brachiocephalic, subclavian, and vertebral vessels. CTA was substituted for MRA in cases where MRA was unavailable. The images were assessed independently by 2 stroke neurologists (S.H.L. and J.M.J.) who were blinded to the available clinical data. Discrepancies were resolved via consensus. The shape of the PICA was noted by the 3-dimensional reconstructed image of the time-of-flight MRA, contrast-enhanced MRA, or CTA. We classified the PICA according to the course of the artery based on a previous report. The PICA originates from the VA and courses around the medulla oblongata from the anterior to the posterior aspect of the brainstem, nearly reaching the foramen of Magendie.[10,11] We measured the angle of the PICA to distinguish its shape. The angle between the VA and the proximal portion of the PICA was measured (Fig 2).

Data Collection

We collected baseline demographic data and clinical information on all study participants; including the magnitude of the PICA angle; age; sex; history of previous stroke; and stroke risk factors, such as hypertension; diabetes mellitus; dyslipidemia; smoking status; and CE sources. All patients underwent transthoracic echocardiography and 24-hour Holter monitoring or continuous stroke unit electrocardiographic monitoring immediately after the stroke in an effort to identify the CE source. Additional transesophageal echocardiography and/or transcranial Doppler monitoring with the saline agitation test were performed if CE stroke was suspected. Coagulopathy work-up was adjusted in stroke patients with young age of onset (<45 years old). The classification of CE stroke was established with the presence of major-risk CE sources for stroke according to the ASCOD phenotyping classification system; sources were defined as: permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<1 month) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetation, or infective endocarditis.[12] Patent foramen ovale was excluded in the absence of in situ thrombus, concomitant pulmonary embolism, or proximal deep venous thrombosis preceding the index cerebral infarction.[12]

Statistical Analysis

The χ^2 test was used to analyze between-group differences. Differences in continuous variables were assessed using Student's *t* test. The relationship between the CE source and

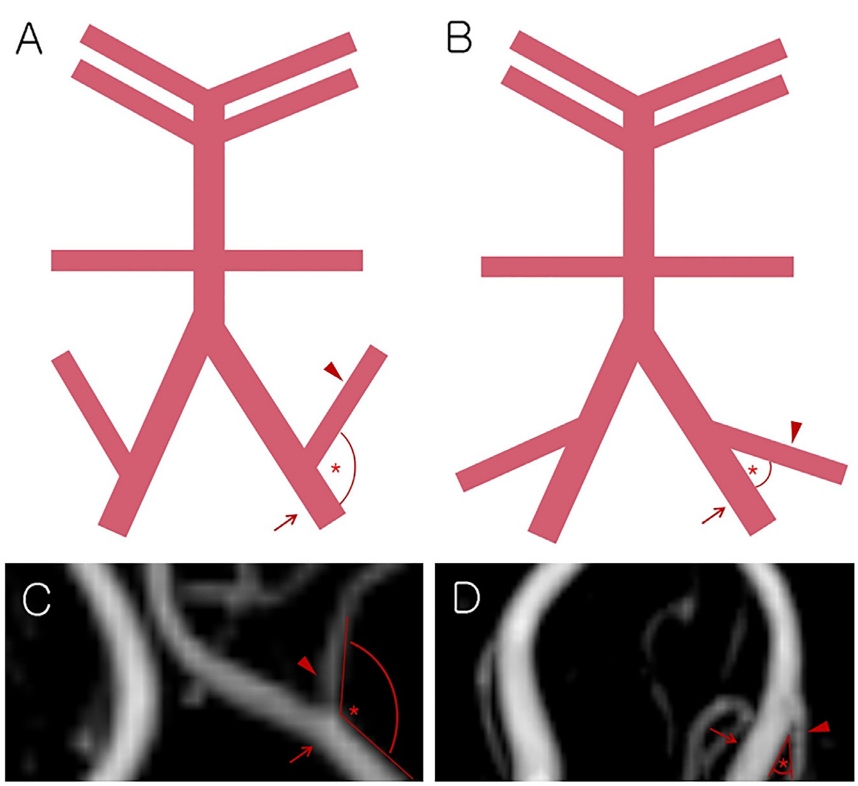

Figure 2. *Schematic diagram of the PICA angle measurement method and representative cases. (A) Obtuse angle, (B) acute angle, (C) obtuse angle, and (D) acute angle. Red arrows = vertebral artery, red arrowheads = PICA, and red star = PICA angle. Abbreviations: PICA, posterior inferior cerebellar artery. (Color version of figure is available online.)*

Table 1. *Characteristics of study participants according to CE source*

Variables	All	CE sources (+)	CE sources (−)	*P* value
	(*N* = 71)	(*N* = 18)	(*N* = 53)	
Age (year)	63.0 ± 15.1	74.3 ± 10.6	59.2 ± 14.6	<.001
Female	23 (32.4)	6 (33.3)	17 (32.1)	.922
Hypertension	32 (45.1)	11 (61.1)	21 (39.6)	.113
Diabetes	16 (22.5)	5 (27.8)	11 (20.8)	.531
PICA angle (degree)	81.6 ± 26.7	101.0 ± 28.1	75.1 ± 23.1	<.001
Previous stroke	7 (9.9)	5 (27.8)	2 (3.8)	.010
Smoking	23 (32.4)	4 (22.2)	19 (35.8)	.386
Hyperlipidemia	29 (40.8)	2 (11.1)	27 (50.9)	.005

Abbreviations: CE, cardioembolism; PICA, posterior inferior cerebellar artery.
Results are expressed as number (column %) or mean ± standard deviation.

risk factors was assessed using univariable and multivariable logistic regression, with CE sources as the response variable and related factors as the explanatory variables. The multivariable logistic regression analysis included all potential predictor variables with a *P* value less than .05 from the univariable analyses in the model, and variables that were known risk factors for stroke were subjected to multiple logistic regression analysis to identify independent predictors for the CE sources.

To compare the ability of PICA angle measurements to accurately classify subjects with various outcomes, we evaluated the area under the receiver operating characteristic (ROC) curve (AUC), which helped to determine the cut-off value of the PICA angle that predicted the CE sources. We used Youden's index (MedCalc 16.4.1 Software, Mariakerke, Belgium) to obtain the optimal cut-off point.

The significance level was defined as a *P* value less than .05. All statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient Demographics

Between February 2014 and December 2017, 5210 patients were admitted to the stroke centers of the 3 hospitals for an ischemic stroke or transient ischemic attack. Of these, 159 had an acute ischemic lesion that was limited to unilateral PICA territory in the initial diffusion-weighted MRI. Six of the 159 patients were excluded because they did not undergo MRA or CTA. Among the remaining 153 patients, 91 had normal brachiocephalic, subclavian, and vertebral arteries on MRA or CTA. Of these, 71 cases were finally included owing to good visualization of the proximal portion of the PICA via MRA or CTA.

Table 1 presents the demographic characteristics of patients with isolated unilateral PICA territory infarction according to CE sources. There were significant between-group differences in age, previous stroke, hyperlipidemia, and PICA angle. Patients with a CE source were older (74.3 ± 10.6 versus 59.2 ± 14.6 years, $P < .001$) and had larger PICA angles (81.6 ± 26.7° versus 101.0 ± 28.1°, $P < .001$). In contrast, patients without a CE source had more hyperlipidemia ($P = .005$). The other variables did not differ between the 2 groups.

Analysis of Outcomes

Multivariable logistic regression analysis for CE sources as a response variable was performed. The multivariable analysis (Table 2) showed that age (OR 1.086, 95% CI

Table 2. *Multiple logistic regression analysis for PICA infarction with CE sources*

Variables	CE, unadjusted OR (95% CI)	*P* value	CE, adjusted OR (95% CI)*	*P* value
Age (year) (per 1 year ↑)	1.086 (1.014-1.164)	.048	1.083 (1.001-1.171)	.048
Hyperlipidemia	.908 (.104-7.904)	.930	.527 (.048-5.770)	.600
Previous stroke	6.218 (.856-55.157)	.071	6.860 (.834-56.404)	.073
PICA degree (per 1° ↑)	1.054 (1.015-1.095)	.007	1.055 (1.015-1.096)	.007
Hypertension			1.352 (.271-6.745)	.713
Sex			2.257 (.409-12.443)	.350
Smoking			1.237 (.163-9.413)	.837
Diabetes			1.046 (.156-7.033)	.963

Abbreviations: CE, cardioembolism; CI, confidence interval; OR, odds ratio; PICA, posterior inferior cerebellar artery.
*Adjusting for PICA angle and all variables associated with stroke risk factors such as age, sex, hyperlipidemia, previous stroke, hypertension, and smoking.

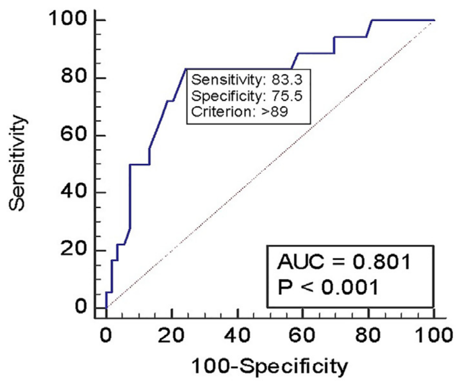

Figure 3. *ROC analysis of the PICA angle and CE source in cases involving unilateral PICA territory infarction. The maximum Youden's index is shown using the arrows. Abbreviations: CE, cardioembolic; PICA, posterior inferior cerebellar artery; ROC, receiver operating characteristic.*

1.014-1.164) and PICA angle (OR 1.054, 95% CI 1.015-1.095) were independently associated with the risk of having CE sources after adjusting for potential confounders.

In order to determine the accuracy of the PICA angle for predicting CE sources, an ROC curve was created, and the AUC was calculated (Fig 3). The AUC for the PICA angle was .801 (95% CI .677-.925, $P < .001$, sensitivity 83.3%, specificity 75.5%). Youden's index for maximum diagnostic accuracy was determined. The optimal cut-off value between the PICA angle and CE source obtained using Youden's index was 89°.

We classified the PICA shape based on the optimal cut-off value (89°) obtained using the Youden's index (Table 3). In the group with CE sources, the PICA angle exceeded 89° in 83.3% of cases, while the PICA angle was less than 89° in only 16.7% of cases ($P < .001$).

Discussion

The present study investigated whether CE infarction occurred in the unilateral PICA territory without relevant vessel stenosis and assessed the incidence of infarction according to the magnitude of the PICA angle. An obtuse PICA angle (>89°) was the strongest predictor of unilateral PICA infarction in patients with high-risk CE sources (83.3%).

The likelihood of a CE source in cases involving unilateral PICA territory infarction without related vascular stenosis was observed in 18 of 71 patients (25.3%). This figure is consistent with the frequency reported in previous studies.[13-17] PICA angle was associated with significantly increased odds of finding a CE source in the multiple logistic regression analysis adjusted for PICA angle and all variables associated with stroke risk factors. This implies that the probability of finding the CE source increased with an increasing angle of the PICA with the VA.

ROC analysis of the PICA angle and CE source yielded an AUC of .801 (95% CI .677-.925, $P < .001$, sensitivity 83.3%, specificity 75.5%). The optimal cut-off value obtained using the Youden's index was 89°. In other words, if the PICA angle exceeds 89°, a more detailed heart examination will be required to find the CE source. In this study, a CE source was identified in 83.3% of cases when the PICA angle exceeded 89°.

Finding the CE sources is very important in acute stroke patients because early confirmation of the diagnosis of a CE as the cause of cerebral infarction enables early anticoagulation therapy for adequate secondary prevention.[18-20] A CE work-up that can identify the cause of the infarction includes transthoracic echocardiography, 24-hour Holter monitoring, and occasionally transesophageal echocardiography.[21,22] However, due to the time involved and the expensive nature of the tests, such a thorough examination of all stroke patients is impractical. In particular, neuroimaging findings that support CE stroke include simultaneous or sequential strokes in different arterial territories; however, as cerebral infarction occurring in the area of a single blood vessel is less likely to have a CE cause, it is difficult to perform a CE work-up in detail.[23] Therefore, factors that predict the likelihood of CE infarction should be determined. If a factor is consistently observed, a more detailed CE work-up with techniques, such as contrast-enhanced transcranial Doppler, transthoracic echocardiography, transesophageal echocardiography, and Holter monitoring, will be required.

Associated vascular stenosis was absent in all patients enrolled in this study. If a CE source is found, the patient is considered to have a CE infarction, and anticoagulation therapy is needed. Thus, finding the CE source in acute stroke patients is very important.

Table 3. *Comparison of PICA infarction with and without CE source according to the optimal cut-off value*

Variables	All	CE source (+)	CE source (−)	*P* value
	(*N* = 71)	(*N* = 18)	(*N* = 53)	
PICA angle				<.001
≤89	43	3 (16.7)	40 (75.5)	
>89	28	15 (83.3)	13 (24.5)	

Abbreviations: CE, cardioembolism; PICA, posterior inferior cerebellar artery.
Results are expressed as number (column %) or mean ± standard deviation.

This study had several limitations. First, although the study involved the use of a multicenter database, the study included only a small number of patients owing to the strict inclusion/exclusion criteria. Thus, generalizing the results of this study will be challenging. Second, there were limitations owing to the use of clinical registry data; this resulted in several biases in terms of patient selection, recording, completeness of data, and assessment of outcome. The findings must be further confirmed in prospective multicenter studies with larger samples. Third, stroke etiology in the 53 patients without an identified CE sources was unclear. Hidden atrial fibrillation, complex aortic atheroma, and atrial cardiopathy, which have recently been considered plausible CE sources, were not completely evaluated through routine work-up. However, a previous study has reported that in patients with in situ atherosclerotic disease, cerebellar infarcts usually involved the PICA territory.[2] Hyperlipidemia is an important risk factor for atherosclerosis, which is the major cause of cerebrovascular disease.[24,25] In the present study, hyperlipidemia was more frequent in patients with PICA infarction without CE sources (50.9% versus 11.1%, $P = .005$). Therefore, a significant number of patients with PICA infarction without CE sources might have in situ atherosclerotic occlusion of the PICA itself. Fourth, identification of a CE source does not mean that the CE source is the cause of the infarction. However, no patients enrolled in this study had associated vascular stenosis. Therefore, a CE source found in these patients would be considered the cause of the infarction, and anticoagulation therapy would be necessary. Finally, from the hemodynamic viewpoint, besides the PICA angle, the PICA diameter itself or its ratio with the VA diameter can also be an important factor in the flow direction of the embolus. Due to the technical limitations of MRA, maximum intensity projection image, volume rendering image, high-resolution MRI, or transfemoral cerebral angiography can be used to accurately measure the PICA diameter. Studies should be conducted to investigate the relationship between CE sources and PICA diameter itself or its ratio with the VA diameter using these imaging techniques or methods in the future.

In conclusion, an obtuse PICA angle was the strongest predictor of unilateral PICA territory infarction in the absence of vascular stenosis. If the PICA angle exceeds 89°, it is important to search for a CE source to determine the appropriate treatment.

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