Atherosclerotic Plaque Locations may be Related to Different Ischemic Lesion Patterns

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Abstract

Background: Atherosclerosis of the internal carotid artery (ICA) are an important cause of ischemic stroke. Artery-to-artery embolism is the major stroke mechanism in patients with atherosclerotic carotid disease. We hypothesized that the atherosclerotic ICA geometry and plaque location would be associated with the lesion pattern in acute ischemic stroke.

Methods: Ischemic stroke patients with symptomatic proximal ICA disease (> 50% diameter stenosis) were enrolled. The carotid plaque location was divided into high-apical and low-body types. The geometric parameters of the ICA (angles between arteries) were measured; moreover, ischemic lesion patterns were classified according to the number, location, and size of the lesions. Factors associated with plaque location and lesion pattern (dichotomized by size) were investigated.

Results: A total of 93 patients (31 high-apical plaques and 62 low-body plaques) were investigated. In patients with low-body plaques, hyperlipidemia was more prevalent and the common carotid artery (CCA)-ICA angle was wider (162.3 ± 9.8° vs. 167.7 ± 10.4°, $p = 0.019$). Low-body plaques more frequently appeared as small scattered or cortical lesions (54.8% vs. 32.3%, $p = 0.040$), whereas high-apical plaques more frequently appeared as a large lesion with additional lesions (38.7% vs. 11.3%, $p = 0.002$). Low-body plaques (odds ratio 3.106, 95% confidence interval 1.105–8.728, $p = 0.032$) was independently associated with the small lesions only pattern.

Conclusions: Low-body plaques more frequently present small-scattered lesions, whereas high-apical plaques more frequently present a large lesion with additional lesions. A wide CCA-ICA angle is associated with low-body plaque of the carotid artery.

Background

Atherosclerosis of carotid artery is one of the major causes of ischemic stroke. Previous study showed that artery-to-artery embolism is the major stroke mechanism in the patients with atherosclerosis of carotid artery [1]. Especially, rupture of ulcerative plaque with subsequent embolization of thrombus was associated with ischemic stroke in these patients besides degree of stenosis [2, 3]. However, these risk factors are inexplicable for the distribution and size of ischemic lesions due to artery-to-artery embolism caused by atherosclerosis of carotid artery among individual patients. Blood flow may be an important factor affecting lesion size and pattern, as itself can influence the activation of platelets and coagulation cascade and dislodging thrombus [4, 5].

Atherosclerotic plaque of carotid artery was associated with old age, male sex, and hyperlipidemia [1]. However, these risk factors are unexplainable for the specific location of plaque in the carotid artery among individual patients. Besides these general risk factors, hemodynamics may also affect the location of plaque within the carotid artery. Some studies demonstrated that high wall shear stress (WSS) has been associated with plaque formation at the apex of the carotid artery and low WSS was related to plaque formation at the bulb of the carotid artery [6, 7]. Moreover, the geometric properties of the carotid

artery (i.e., bifurcation angle and radius), which have been proposed as factors regulating WSS, are associated with the location of plaque in the carotid artery [8, 9]. According to the location of plaques affecting the WSS inside the carotid artery, the nature and size of emboli from the atherosclerotic stenotic lesion may be different.

In this study, we aimed to investigate the lesion patterns of acute ischemic stroke on diffusion-weighted imaging (DWI), according to the location of carotid plaques.

Methods

Subjects

This study was a retrospective analysis of a prospectively collected database of acute ischemic stroke patients (within 7 days from stroke onset) between January 2013 and December 2017. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, patients classified as large artery atherosclerosis with symptomatic proximal internal carotid artery (pICA) disease were enrolled [10]. Symptomatic pICA disease was considered to be present when vascular stenosis of the pICA (> 50% diameter stenosis) was the culprit of index middle cerebral artery (MCA) or anterior cerebral artery (ACA) infarction [11].

We excluded patients with (1) embolic sources from the heart (e.g., atrial fibrillation or valvular heart disease) or the aorta, (2) other uncommon etiologies such as dissection or moyamoya disease, (3) tandem stenotic lesion at the intracranial ICA and MCA or ACA, and (4) contrast enhanced magnetic resonance angiography (MRA) data that do not allow the assessment of geometric properties (e.g., complete occlusion, poor MRA quality). The institutional review board of Kyung Hee University Hospital approved this study but waived the need for informed consent because of its retrospective nature.

Clinical data and neuroimaging

Demographic characteristics, vascular risk factors, concurrent medication, and baseline laboratory results were obtained from the prospectively acquired stroke database.

On the first day of admission, the patients underwent magnetic resonance imaging and MRA in the following sequence: DWI, fluid attenuated inversion recovery imaging, gradient echo imaging, T1- and T2-weighted imaging, and intracranial and extracranial contrast enhanced MRA.

The patterns of infarction on DWI were classified according to the number, location, and maximum diameter of lesions [12, 13]. First, according to number, the lesions were classified as single or multiple lesions. Second, according to size, the lesions were divided into large (≥ 15 mm) and small (< 15 mm) lesions based on the maximum diameter. Third, according to location, single lesions were classified into cortical (small), subcortical (small or large), and cortico-subcortical (large) lesions. Multiple lesions were classified into small scattered lesions or a large lesion with additional lesions. The topography of ischemic lesions according to the vascular territory was determined with reference to published templates

[14]. For further analysis, lesion pattern was dichotomized according to the presence (large lesion including group) or absence (small lesions only group) of a large lesion.

Carotid plaque and geometry

The presence and location of plaque and the stenosis degree in the pICA were assessed on contrast enhanced MRA. The location of atherosclerotic plaques of the carotid artery was classified into the high-apical and the low-body plaque. A high-apical plaque was defined as a plaque in the transitional zone of the bulb and the proximal cervical ICA segment with or without the involvement of the body segment. A low-body plaque was defined as a plaque in the transitional zone of the common carotid artery (CCA) and the bulb, which is located mainly in the lower body segment with or without the involvement of the apical segment (Supplementary Fig. 1). For the differentiation of the type of enlarged plaques, the location of the main plaque component and the level of the most severe stenosis were considered [7].

The geometry of the carotid artery was quantitatively analyzed by modifying previously published methods [15]. As illustrated in Supplementary Fig. 1, the ICA-external carotid artery (ECA) angle was defined as the angle between the projections of the ICA0-ICA5 and ECA0-ECA5 vectors onto the bifurcation plane. The CCA-ICA angle and the CCA-ECA angle were defined similarly. Moreover, ICA planarity was defined as the angle between the out-of-plane components of the CCA and ICA vectors. The ICA-to-CCA diameter ratio was calculated as the ICA5 diameter divided by the CCA5 diameter.

Furthermore, geometrical factors which may affect the risk of embolism or vulnerability of plaque; 1) stenosis degree measured by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, 2) presence of ulcer which defined as a niche in the plaque surface of > 2 mm in depth on contrast enhanced extracranial MRA [16], 3) carotid webs which considered as a thin intraluminal filling defect along the posterior wall of the carotid bulb in oblique sagittal reformats image on contrast enhanced extracranial MRA [17], or 4) ICA kinking which is an extreme form of tortuous ICA with angulation of the vessel's axis of 90° or less [18] were also investigated and considered.

Statistical methods

Demographic characteristics, vascular risk factors, concurrent medication, laboratory findings, geometrical factors, and ischemic lesion patterns were compared between the two plaques locations. The Pearson chi-square, independent *t*-test and Mann-Whitney U-test were used as appropriate. Multivariable binary logistic regression was performed to investigate the independent association between the small lesions only pattern and the type of plaque or the geometric properties of the carotid bifurcation. Odds ratios (ORs) were obtained with 95% confidence intervals (95% CIs). A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp. Armonk, NY, USA).

Results

From our initial database including 3061 patients with acute ischemic stroke, 657 (21.5%) patients were classified as having large artery atherosclerosis according to the TOAST classification. Among them, 117 (17.8%) patients had symptomatic pICA disease. The final study population included 93 patients, after excluding patients with complete occlusion in the carotid artery, those with no DWI or MRA data, and those with poor MRA quality.

The mean age of the 93 patients was 72.0 ± 8.3 years, and 80.6% of them were men. High-apical plaque was observed in 31 (33.3%) patients, whereas low-body plaque was observed in 62 (66.7%) patients.

Characteristics of patients with high-apical and low-body plaques

Table 1 shows that the incidence of a history of hyperlipidemia were significantly higher in patients with low-body plaques than in those with high-apical plaques ($p = 0.022$). The CCA-ICA angle was significantly wider in patients with low-body plaques than in those with high-apical plaques (162.3 ± 9.8° vs. 167.7 ± 10.4°, $p = 0.019$; Table 2). In multivariable analysis, relative to high-apical plaques, wider CCA-ICA angle (OR 1.061, 95% CI 1.010–1.115, $p = 0.018$) and narrow ICA-ECA angle (OR 0.961, 95% CI 0.925–0.999, $p = 0.043$) was independently associated with low-body plaques (Supplementary Table 1 and Supplementary Table 2).

Table 1
Baseline demographics and clinical characteristics of patients with high-apical and low-body plaques

Variables	High-apical type (n = 31)	Low-body type (n = 62)	*p* value
Age, y	72.7 ± 6.8	71.7 ± 9.0	0.588
Male sex	23 (74.2)	52 (83.9)	0.265
Hypertension	25 (80.6)	48 (77.4)	0.721
Diabetes mellitus	12 (38.7)	21 (33.9)	0.646
Hyperlipidemia	15 (48.4)	45 (72.6)	0.022
Smoking	17 (54.8)	36 (58.1)	0.767
History of stroke or TIA	11 (35.5)	15 (24.2)	0.253
Previous medication	12 (38.7)	30 (48.4)	0.377
Antiplatelets	9 (29.0)	25 (40.3)	0.287
Statin			
NIHSS	3.0 [2.0–10.0]	4.0 [2.0–6.2]	0.787
Admission	2.0 [1.0–6.0]	3.0 [1.7–5.2]	0.519
Discharge			

Values are expressed as number (%), mean ± standard deviation, or median [interquartile range].

BUN, blood urea nitrogen; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; WBC, white blood cell

Variables	High-apical type (n = 31)	Low-body type (n = 62)	*p* value
Laboratory findings			
WBC, per mm^2	9144.2 ± 5383.2	8514.7 ± 2669.0	0.452
Hematocrit	38.8 ± 6.2	40.6 ± 4.9	0.119
Platelet, $\times 10^3/mm^2$	264.0 ± 115.2	236.8 ± 65.8	0.152
Glucose, mg/dL	124.9 ± 36.8	137.3 ± 53.6	0.262
Glycated hemoglobin (HbA1c)	6.3 ± 1.1	6.5 ± 1.4	0.610
Total cholesterol, mg/dL	159.5 ± 55.9	170.7 ± 51.4	0.341
HDL cholesterol, mg/dL	37.7 ± 8.8	40.7 ± 11.4	0.202
Triglyceride, mg/dL	132.6 ± 80.1	146.3 ± 104.4	0.523
LDL cholesterol, mg/dL	106.4 ± 41.7	108.8 ± 39.9	0.785
BUN, mg/dL	17.0 ± 6.0	18.6 ± 7.4	0.303
Creatinine, mg/dL	0.9 ± 0.3	1.0 ± 0.7	0.679
CRP, mg/dL	1.2 ± 3.9	0.7 ± 2.1	0.393

Values are expressed as number (%), mean ± standard deviation, or median [interquartile range].

BUN, blood urea nitrogen; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; WBC, white blood cell

Table 2
Carotid geometry and lesion patterns among patients with high-apical and low-body plaques

	High-apical type (n = 31)	Low-body type (n = 62)	*p* value
Carotid geometry			
ICA-ECA angle, °	28.4 ± 14.9	22.8 ± 10.0	0.067
CCA-ICA angle, °	162.3 ± 9.8	167.7 ± 10.4	0.019
CCA-ECA angle, °	168.8 ± 12.4	169.1 ± 12.1	0.869
ICA-to-CCA diameter ratio	0.56 ± 0.13	0.55 ± 0.12	0.832
ICA planarity	17.0 ± 8.9	18.1 ± 10.7	0.625
ICA stenosis severity (NASCET)	69.2 ± 11.4	64.6 ± 13.6	0.105
Kinking of ICA	2 (6.5)	3 (4.8)	0.999
Ulceration of plaque	16 (51.6)	35 (56.5)	0.658
Carotid web	0	0	N/A
Lesion pattern on DWI			
Small single cortical lesion	2 (6.5)	2 (3.2)	0.598
Small (< 15 mm) single subcortical lesion	1 (3.2)	4 (6.5)	0.662
Small (< 15 mm) multiple scattered lesion	10 (32.3)	34 (54.8)	0.040
	5 (16.1)	9 (14.5)	0.999
Large single cortico-subcortical lesion	1 (3.2)	6 (9.7)	0.418
Large single subcortical lesion	12 (38.7)	7 (11.3)	0.002
Large lesion with additional lesions			

Values are expressed as number (%) or mean ± standard deviation.

CCA, common carotid artery; DWI, diffusion-weighted imaging; ECA, external carotid artery; ICA, internal carotid artery; N/A, not available; NASCET, North American Symptomatic Carotid Endarterectomy Trial

Carotid geometry and lesion pattern

Among the patients, with respect to the distribution of lesion patterns in the two groups, small scattered lesions were more frequently observed in patients with low-body plaques (32.3% vs. 54.8%, $p = 0.040$), whereas a large lesion with additional lesions more frequently appeared in patients with high-apical plaques (38.7% vs. 11.3%, $p = 0.002$; Table 2). In multivariable analysis, a low-body plaque was the only factor independently associated with the small lesions only pattern (OR 3.106, 95% CI 1.105–8.728, $p = 0.032$; Table 3 and Supplementary Table 3).

Table 3
Multivariable analysis of factors associated with the small lesions only type

	Model 1, unadjusted Odds ratio (95% CI)	Model 2, §Odds ratio (95% CI)	Model 3, †Odds ratio (95% CI)
ICA-ECA angle, °	0.998 (0.965–1.032)	0.999 (0.959–1.040)	0.999 (0.960–1.042)
CCA-ICA angle, °	0.978 (0.940–1.018)	0.970 (0.927–1.015)	0.970 (0.927–1.016)
CCA-ECA angle, °	1.021 (0.986–1.057)	1.029 (0.987–1.073)	1.027 (0.984–1.072)
Low-body plaque	2.571 (1.041–6.087)*	3.058 (1.107–8.449)*	3.106 (1.105–8.728)*
* $p < 0.05$.			
§ Adjusted for hypertension, low-density lipoprotein cholesterol, and white blood cell count.			
† Adjusted for age, male sex, hypertension, low-density lipoprotein cholesterol, and white blood cell count.			
CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; ICA, internal carotid artery			

Discussion

In the present study, we found that the CCA-ICA angle was wider in patients with low-body plaques. These low-body plaques were more associated with small scattered lesions and independently associated with having only small lesions with diameter less than 15 mm. Patients with high-apical plaques had a narrow CCA-ICA angle and had more chance of having a large ischemic lesion.

A previous study proposed that hyperlipidemia was more associated with the low-body type [7]. These finding was in concordance with our findings showing that a history of hyperlipidemia was associated with low-body plaques. However, hyperlipidemia usually act more systemically and still have a limitation in explaining the specific location of atherosclerosis. A local factor such as vascular geometry may influence where atherosclerosis may develop. From a previous study with computational fluid dynamics of carotid artery, the bifurcation angle showed a significant negative correlation with the WSS in the inner and outer wall of the ICA, which was explained by the loss of energy. Especially, as the CCA-ICA angle decreased, the WSS in the inner wall of ICA decreased more rapidly than that in the outer wall [19]. These may explain our result showing that a decreased CCA-ICA angle was independently associated with the presence of high-apical plaques. In the majority of cases of high-apical plaques (25 of 31), the plaques were located in the inner curvature in our study, which showed a more rapid decrease in WSS. Furthermore, a second angle exists in those with a decreased CCA-ICA angle, forming a curvature leading to a low WSS in the inner curvature that is prone to atherosclerosis development (Supplementary Fig. 1) [20].

Our result also showed that the lesion patterns on DWI in acute ischemic stroke patients with symptomatic pICA disease were associated with the plaque location, but not the geometry of ICA or the presence of ulcer. Small scattered lesions were associated with low-body plaques of the ICA, whereas the presence of a large lesion with additional lesions was associated with high-apical plaques of the ICA. When dichotomizing the lesion patterns according to the presence or absence of a large lesion, low-body plaques were independently associated with the small lesions only pattern. In high-apical plaques, the bulb exists proximal to the stenotic portion with a back flow causing fluid stagnation and thrombus formation, such as in the appendage of the left atrium [21, 22]. This may cause a large thrombus inside the bulb area, resulting in a large-sized infarction [23]. On the other hand, low-body plaques increase the flow velocity at the bulb area. The high speed flow may induce shear dependent platelet activation and generate multiple small thrombi, resulting in small-scattered lesions (Fig. 1) [24].

Our current study has several limitations. First, its retrospective nature may have caused a selection bias. Second, the number of patients was small and, consequently, some of our results were underpowered, especially the lesion patterns. Third, we analyzed the geometry based on two-dimensional anteroposterior images of three-dimensionally reconstructed MRA images. A three-dimensional analysis of the vascular geometry might strengthen our results. Finally, composition and vulnerability of plaque, the size and composition of the embolus from each stroke mechanism were not confirmed pathologically. Despite these limitations, our results suggest the importance of the vascular geometry in the development of acute stroke with symptomatic pICA disease.

Conclusion

The CCA-ICA angle may be a factor determining the location of atherosclerotic plaques of the carotid artery, probably altering hemodynamics. The different locations of carotid plaques may be one of the reasons for the individual differences in the location of lesions in acute ischemic stroke with symptomatic pICA disease.

List Of Abbreviations

WSS: wall shear stress

DWI: diffusion-weighted imaging

TOAST: Trial of Org 10172 in Acute Stroke Treatment

pICA: proximal internal carotid artery

MCA: middle cerebral artery

ACA: anterior cerebral artery

MRA: magnetic resonance angiography

CCA: common carotid artery

ECA: external carotid artery

NASCET: North American Symptomatic Carotid Endarterectomy Trial

ORs: odds ratios

CIs: confidence intervals

Declarations

Ethics approval and consent to participate:

The institutional review board of Kyung Hee University Hospital approved this study but waived the need for informed consent because of its retrospective nature.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest:

The authors declare that they have no competing interests.

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Authors’ contributions:

Research conception and design, H.G.W., T.J.S., S.H.H., D.I.C., B.J.K.; Data acquisition, H.G.W., S.H.H., E.J.K., D.I.C., B.J.K.; Data analysis and interpretation, H.G.W., T.J.S., S.H.H., E.J.K., D.I.C., B.J.K.; Statistical

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Figures

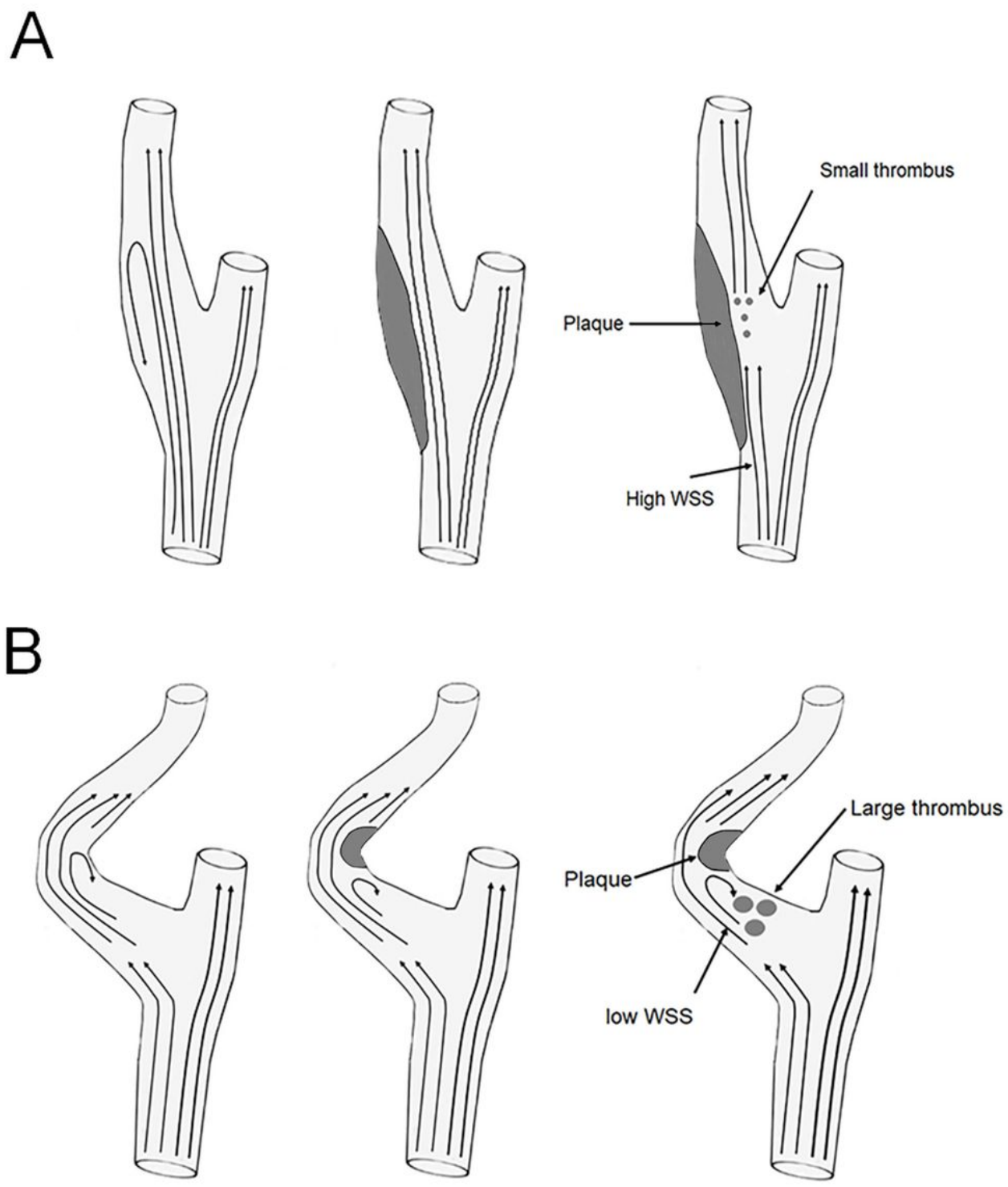

Figure 1

Schematic drawing of plaque and thrombus formation in the carotid artery

Supplementary Files

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