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Patients with Acute Ischemic Cerebrovascular Disease with Coronary Artery Stenosis Have More Diffused Cervicocephalic Atherosclerosis

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Aim: Coronary artery stenosis (CAS) ≥ 50% frequently coexists in patients with acute ischemic cerebrovascular disease (AICVD), which portends unfavorable outcomes. We sought to examine whether patients with AICVD with CAS had more severe and more diffused cervicocephalic atherosclerosis (CA).

Methods: Patients with AICVD were consecutively enrolled and underwent simultaneous computed tomography angiography (CTA) of the coronary and cervicocephalic arteries. A total of 140 patients were divided into "AICVD + CAS" and "AICVD only" groups according to whether CTA showed stenosis of ≥ 50% in at least one coronary arterial segment. The relationship of the presence of CAS with the severity and extent of CA were examined.

Results: The CA severity characteristics, including the presence of stenosis ≥ 50% and the grade of the most severe stenotic segment, were not significantly different between the two groups. Regarding the extent of CA, the presence of stenosis ≥ 50% in both sides (adjusted odds ratio [OR]: 4.29, 95% confidence interval [CI]: 1.67–10.98), both extracranial and intracranial (adjusted OR: 5.26, 95% CI: 2.24–12.35), both anterior and posterior circulation (adjusted OR: 5.29, 95% CI: 2.22–12.64), and the number of stenotic segments ≥ 50% in cervicocephalic arteries (adjusted OR: 1.58, 95% CI: 1.28–1.96) were associated with CAS in patients with AICVD, independently of clinical demographics and CA severity characteristics.

Conclusion: CA was similarly severe in patients with AICVD with and without CAS, but those with CAS had significantly more diffused CA. The extent of CA and CAS were mutual indicators in patients with AICVD, irrespective of CA severity.

Key words: Acute ischemic cerebrovascular disease, Cervicocephalic atherosclerosis, Coronary artery stenosis, Extent, Severity

Introduction

The coronary and cervicocephalic arteries are often simultaneously affected by similar vascular risk factors[1]. About 15% of patients with acute ischemic cerebrovascular disease (AICVD) had a known history of coronary artery disease[2, 3], whereas 18%–33% of patients with AICVD without previous coronary artery disease showed stenosis ≥ 50% on coronary angiography[4-6]. Compared to patients with AICVD with no coronary atherosclerosis, the risk for 2-year combined vascular events was 6.86 times for those with known coronary artery disease, and 4.36 times for those with coronary artery stenosis (CAS) ≥ 50%, but no cardiac symptoms[7]. Furthermore, the rate of stroke recurrence in patients with AICVD increased with the presence of CAS[8]. Evidence shows that the intimal medial thickness of the extracranial carotid

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arteries of patients with CAS progressed three times faster than that of patients with no CAS[9]. Thus, it is reasonable to postulate that CAS would indicate more serious cervicocephalic atherosclerosis (CA), leading to a higher risk of recurrent cerebral ischemic events in patients with AICVD.

Therefore, delineating the CA characteristics in patients with AICVD with CAS can be helpful to partially explain their predisposition to AICVD recurrence and to come up with appropriate monitoring and intervening solutions for patients at higher risk. Prior studies focused mainly on predicting CAS in patients with AICVD without a history of coronary artery disease, and asymptomatic CAS has been shown to be correlated with CA independently of traditional vascular risk factors[4, 10]. However, symptomatic CAS was also an indicator of high vascular risk[7], and CA characteristics in patients with AICVD with both symptomatic and asymptomatic CAS had not been explored. Furthermore, the majority of studies examined the associations between CAS and CA severity[6, 10, 11], while the extent of CA characteristics in patients with concomitant AICVD and CAS were only preliminarily investigated in a narrow range[4, 5]. The prognostic value of the CA extent for patients with AICVD has been highlighted in recent years[12, 13], but how it is related to CAS is still unclear.

Technically, the 192-slice computed tomography (CT) is capable of simultaneously examining the coronary and cervicocephalic arteries with a lower radiation dose than the traditional CT angiography (CTA) of cervicocephalic arteries[14].

Aim

With simultaneous coronary and cervicocephalic CTA, we aimed to test the hypothesis that patients with concomitant AICVD and CAS may have more severe and more diffused CA than patients with AICVD only.

Methods

This was a single-center, cross-sectional study. The hospital ethics committee approved the study and all participants provided informed consent. Patients admitted to our stroke unit from January 01, 2016 to June 30, 2016 were enrolled in this study if they meet the following selection criteria: they were 18–85 years of age; diagnosed with acute ischemic stroke or transient ischemic attack (TIA); and diagnosed within 14 days after the onset of symptoms. Patients with suspected non-atherosclerotic arterial stenosis, such as arterial dissection and vasculitis; cardioembolism or revascularization procedures; poor organ functions or hematologic diseases; and contraindications to CTA, were excluded. Patients who could not tolerate the CTA examination without interpretable images were eventually excluded from the final analysis.

Demographics and Clinical Characteristics

Demographic information, vascular risk factors (hypertension history, diabetes mellitus history, hypercholesterolemia history, smoking, obesity), previous acute ischemic stroke, and coronary artery disease history were recorded during a face-to-face interview. The patient was considered as smoking if they actively smoked within the last 12 months before this hospital admission[15]. Obesity was defined as a body mass index ≥ 30 kg/m^2 at the time of admission[16].

The National Institute of Health Stroke Scale was scored to assess the global deficit of the stroke. The Trial of Org 10172 in Acute Stroke Treatment criteria were used to classify acute ischemic stroke[17]. In addition, a stroke caused by aortic arch atherosclerosis was classified as a stroke of large-artery atherosclerosis[18]. All patients underwent standard blood tests, brain magnetic resonance imaging with diffusion-weighted imaging sequence or a CT scan, 12-lead electrocardiogram, and transthoracic echocardiography within 7 days after admission.

Simultaneous Coronary and Cervicocephalic CTA

All CTAs were performed with a dual-source 192-slice CT scanner (Somatom Force, Siemens Healthcare, Forchheim, Germany). Data were acquired in a caudocranial direction from the diaphragm to the vertex. Image acquisition was prospectively triggered by the patient's electrocardiogram and started at 30% or 60% of the R-peak to R-peak interval depending on the patient's heart rate using the Turbo Flash Spiral mode. CT parameters were slice collimation of 192 × 0.6 mm; gantry rotation time 250 ms, and pitch 3.2. Studies were performed with automated tube current modulation (CARE Dose4D, Siemens) using a reference tube current time of 330–450 mAs. The tube voltage ranged from 70 to 90 kV using automated attenuation-based tube voltage selection (CAREkV, Siemens). The amount of contrast material (Ultravist 370 Iodine/ml; Bayer Schering Pharma, Germany) was adjusted according to the body mass index of the patient and ranged between 40 and 50 ml. The contrast agent was injected intravenously through the antecubital vein by a power injector with a 20–22 gage needle at a flow rate of 5 mL/s, followed by a 50-mL saline chaser bolus. The contrast agent application was controlled using the bolus-tracking technique in the ascending aorta (signal

attenuation threshold, 100 HU). Data acquisition was initiated after the threshold was reached in the ascending aorta, with a mean delay of 8 s. Each raw data point was reconstructed with Advanced Model-based Iterative Reconstruction, with a slice thickness of 0.6 mm and an increment of 0.4 mm using a medium smooth reconstruction kernel (Bv36), and transferred to an external workstation (MMWP, Syngo.via, Siemens) to evaluate all CTA datasets. We recorded the dose–length–product (DLP in mGy cm) from the patient protocol for the radiation exposure, which is automatically generated for each examination.

Curved planar reformatting, maximum intensity projection, multiplanar reformatting, and volume rendering images were used to evaluate the coronary and cervicocephalic arteries. The percentage of arterial stenosis was quantified on orthogonal views with an automatic vessel analysis tool according to the North American Symptomatic Carotid Endarterectomy Trial method[19] for the extracranial cervicocephalic arteries and the Warfarin–Aspirin Symptomatic Intracranial Disease Study Trial method[20] for the intracranial cervicocephalic arteries. Cervicocephalic and coronary angiograms were reviewed by two certified radiologists blinded to coronary and CA data.

Coronary Atherosclerosis and CA measurements

The existence of CAS was confirmed when there was stenosis ≥ 50% in at least one coronary arterial segment ≥ 1.5 mm in diameter[4]. Patients with an existing stent or a coronary artery bypass graft were considered to have CAS for this study, even their stenotic percentage could not be determined accurately. CAS without cardiac symptoms (stable angina or acute coronary artery syndrome) was defined as asymptomatic CAS.

The cervicocephalic arteries were divided into eight segments, including three extracranial segments (common carotid, extracranial carotid, extracranial vertebral arteries), two proximal intracranial segments (intracranial carotid, intracranial vertebrobasilar arteries), and three distal intracranial segments (anterior cerebral, middle cerebral, posterior cerebral arteries). Intracranial arterial stenosis was considered atherosclerotic if CTA revealed characteristics of lipid, mixed, or calcified plaques, or the patient had at least two of the following vascular risk factors: hypertension, diabetes mellitus, hypercholesterolemia, smoking, history of peripheral artery disease, history of coronary artery disease, preexisting atherosclerotic stenosis (>20%) in another location, or the presence of aortic plaques[21].

CA was evaluated by the severity and extent of stenosis. The presence of stenosis ≥ 50% in the cervicocephalic arteries and the grade of the most severe stenotic segment (0 for no stenosis; 1 for <50% stenosis; 2 for ≥ 50% and <70% stenosis; 3 for ≥ 70% stenosis; 4 for occlusion) were utilized to reflect the CA severity. Whether there was stenosis ≥ 50% in both sides, both extracranial and intracranial, in both anterior and posterior circulation, as well as the number of stenotic segments ≥ 50% in the cervicocephalic arteries, yielded a measure of CA extent.

Grouping of Study Subjects

After the procedure of simultaneous coronary and cervicocephalic CTA, patients were divided into "AICVD + CAS" and "AICVD only" groups according to whether CAS existed. In the subgroup analysis of patients with both AICVD and CAS, they were categorized as "AICVD with asymptomatic CAS" or "AICVD with symptomatic CAS" according to whether cardiac symptoms had presented.

Statistical Analysis

All statistical tests were performed using SPSS software (v17.0; IBM, Armonk, NY, United States). A P value <0.05 was considered statistically significant.

Clinical demographics and CA characteristics were compared between "AICVD + CAS" and "AICVD only" groups. Data were presented as the mean ± standard deviation for continuous variables, count (percentage) for categorical variables, and median (quartile 25%, quartile 75%) for ordinal variables. Student's t test was used for continuous variables that are normally distributed, the Mann–Whitney U test for continuous variables that are not normally distributed, the chi-squared test for unordered categorical variables, and the rank sum test for ordinal variables.

To assess the independent associations, each CA characteristic was entered into a multivariate logistic analysis model on those demographic and clinical characteristics whose p value was <0.10 in univariate analysis. Adjusted odds ratios (ORs) for the presence of CAS were calculated with 95% confidence intervals (CIs). Multivariate logistic regression analysis was also performed to explore the age- and sex-adjusted indicative value of CAS for the presence of various CA extent characteristics.

In the predefined subgroup analysis of patients with AICVD with CAS, CA severity and extent characteristics were compared between the "AICVD with asymptomatic CAS" and "AICVD with symptomatic CAS" groups.

Results

A total of 179 patients with AICVD were admitted to the stroke unit. Eight patients whose symptoms

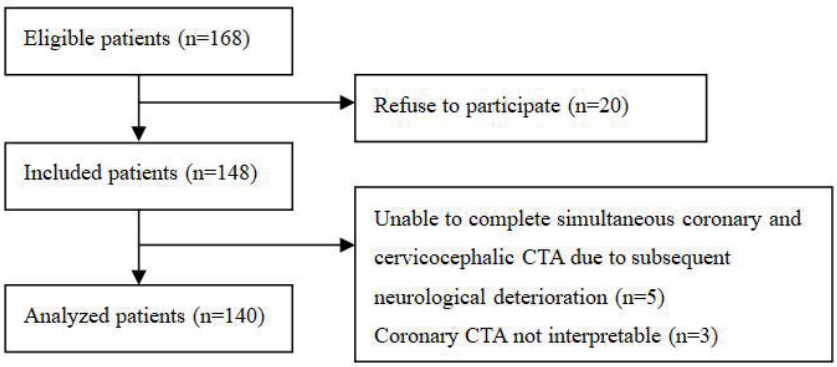

Fig. 1. Flowchart of patient's enrollment

had lasted for >14 days before admission, two patients who had cardioembolic AICVD, and one patient with suspected arterial dissection were not eligible for this study. Among the 168 eligible patients, 20 refused to participate. Of the 148 included patients, 5 could not undergo the simultaneous coronary and cervicocephalic CTA because of subsequent neurological deterioration and three patients' CTA images were not interpretable. The remaining 140 patients were finally included in the analysis. The excluded patients were not significantly different from the patients finally included for analysis in demographics and clinical characteristics (**Fig. 1**).

The study subjects (132 with acute ischemic stroke and eight with TIA) had an average age of 59.3 years, with males being predominant (82.1%) (**Table 1**). Cervicocephalic atherosclerotic stenosis of any grade was observed in 126/140 (90.0%) patients, while stenosis ≥ 50% was revealed in 111/140 (79.3%) patients (**Table 2**). CAS ≥ 50% was detected in 44/140 (31.4%; including three patients with coronary stenting and two patients with coronary artery bypass grafting) patients, and 65.9% of the patients with CAS were asymptomatic. The mean DLP for simultaneous coronary and brain blood-supplying arterial CTA was 125.9 ± 30.7 mGy × cm.

Comparisons of Clinical Demographic Characteristics

Patients with CAS were more likely to be male (93.2% vs. 77.1%, $p=0.021$), have higher systolic blood pressure on admission (median 160 vs. 149 mmHg, $p=0.044$), and have positive coronary artery disease history (34.1% vs. 7.3%, $p<0.001$) than those without CAS. The two groups were similar in other demographics and clinical characteristics (**Table 1**).

Relationship of CA Severity and Extent with CAS

Compared to patients with AICVD only, the group with concomitant AICVD and CAS were more likely to have stenosis ≥ 50% in both sides (68.2% vs. 38.5%, $p=0.001$), in both extracranial and intracranial arteries (56.8% vs. 21.9%, $p<0.001$), and in both anterior and posterior circulation (61.4% vs. 26.0%, $p<0.001$), and the number of ≥ 50% stenotic segments tended to be larger (median 4 vs. 2, $p<0.001$). Regarding the CA severity characteristics, the prevalence of stenosis ≥ 50% in the cervicocephalic arteries and the grade of the most severe stenotic segment were not significantly different between the two groups (**Table 2**).

After adjusting for clinical demographic variables whose p value was <0.10 in univariate analysis (age, sex, history of coronary artery disease, systolic blood pressure on admission, and glycosylated hemoglobin level), the aforementioned CA extent characteristics were still correlated with CAS in patients with AICVD, whereas no independent relationship was observed between CAS and the CA severity characteristics (**Table 3** Adjusted OR1). Furthermore, the presence of CAS was significantly associated with various CA extent characteristics, irrespective of the grade of the most severe stenotic segment (**Table 3** Adjusted OR2). Consistent results were obtained with the additional adjustment of AICVD subtype in the multivariate logistic regression analysis (**Supplemental Table 1**).

Indicative Value of CAS for Diffused CA

After adjusting for age and sex, multivariate logistic regression analysis showed that the presence of CAS significantly increased the risk of having stenosis ≥ 50% in both sides (adjusted OR=3.03, 95% CI: 1.36–6.75, $p=0.007$), in both extracranial and intracranial arteries (adjusted OR=4.08, 95% CI: 1.83–9.10, $p=0.001$), and both anterior and posterior circulation (adjusted OR=4.09, 95% CI: 1.84–9.08,

Table 1. Comparisons of clinical demographic characteristics between AICVD patients with and without CAS

Characteristics	Total (n=140)	AICVD + CAS (n=44)	AICVD only (n=96)	p value
Age (year, X ± S)	59.3 ± 10.4	61.5 ± 9.4	58.3 ± 10.7	0.087
Male (n, %)	115 (82.1)	41 (93.2)	74 (77.1)	0.021*
History of HTN (n, %)	87 (62.1)	30 (68.2)	57 (59.4)	0.319
History of DM (n, %)	50 (35.7)	20 (45.5)	30 (31.3)	0.103
History of HLP (n, %)	27 (19.3)	5 (11.4)	22 (22.9)	0.108
Smoking (n, %)	71 (50.7)	26 (59.1)	45 (46.9)	0.180
Obesity (n, %)	8 (5.7)	2 (4.5)	6 (6.3)	0.991
History of AIS (n, %)	33 (23.6)	11 (25.0)	22 (22.9)	0.787
History of CAD (n, %)	22 (15.7)	15 (34.1)	7 (7.3)	<0.001*
NIHSS on admission [M (Q25, Q75)]	3 (1,5)	3 (1,5)	3 (1,6)	0.619
AICVD subtype				0.340
TIA	8 (5.7)	5 (6.8)	3 (5.2)	
Stroke of large-artery atherosclerosis	85 (60.7)	55 (68.2)	30 (57.3)	
Stroke of small-vessel occlusion	32 (22.9)	26 (13.6)	6 (27.1)	
Stroke with two or more causes identified	15 (10.7)	10 (11.4)	5 (10.4)	
SBP on admission [mmHg, M (Q25, Q75)]	150 (136, 161)	160 (140, 172)	149 (135, 160)	0.044*
DBP on admission [mmHg, M (Q25, Q75)]	86 (80, 92)	89 (80, 99)	85 (80, 92)	0.163
HbA1C [%, M (Q25, Q75)]	5.75 (5.33, 7.10)	6.20 (5.40, 7.50)	5.70 (5.30, 6.80)	0.077
FBG [mmol/L, M (Q25, Q75)]	5.62 (5.04, 6.92)	5.71 (5.06, 7.08)	5.52 (4.97, 6.72)	0.582
Triglycerides [mmol/L, M(Q25, Q75)]	1.36 (0.99, 1.85)	1.46 (0.94, 2.07)	1.32 (1.01, 1.84)	0.782
LDL-C (mmol/L, X ± S)	2.48 ± 0.88	2.60 ± 0.97	2.43 ± 0.84	0.274
HDL-C (mmol/L, X ± S)	1.09 ± 0.29	1.06 ± 0.27	1.10 ± 0.29	0.481
hsCRP [mg/L, M (Q25, Q75)]	3.56 (1.36, 5.92)	3.18 (1.21, 10.12)	3.71 (1.40, 5.70)	0.844

*p<0.05 was considered statistically significant.
Abbreviations: AICVD=acute ischemic cerebrovascular disease; CAS=coronary artery stenosis ≥ 50%; HTN=hypertension; DM= diabetes mellitus; HLP=hyperlipidemia; AIS=acute ischemic stroke; CAD=coronary artery disease; NIHSS=National Institute of Health Stroke Scale; TIA=transient ischemic attack; SBP=systolic blood pressure; DBP=diastolic blood pressure; HbA1C=glycosylated hemoglobin; FBG=fasting blood glucose; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; hsCRP=hypersensitive C reactive protein.

Table 2. Comparisons of CA characteristics between AICVD patients with and without CAS

Characteristics	Total (n=140)	AICVD + CAS (n=44)	AICVD only (n=96)	p value
CA Severity				
Presence of stenosis ≥ 50% (n, %)	111 (79.3)	37 (84.1)	74 (77.1)	0.342
Grade of the most severe stenotic segment [M (Q25, Q75)]	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.175
CA Extent				
Presence of stenosis ≥ 50% in both sides (n, %)	67 (47.9)	30 (68.2)	37 (38.5)	0.001*
Presence of stenosis ≥ 50% in both extracranial and intracranial arteries (n, %)	46 (32.9)	25 (56.8)	21 (21.9)	<0.001*
Presence of stenosis ≥ 50% in both anterior and posterior circulation (n, %)	52 (37.1)	27 (61.4)	25 (26.0)	<0.001*
Number of stenotic segments ≥ 50% [n, M (Q25, Q75)]	2 (1,4)	4 (1, 6)	2 (1, 3)	<0.001*

*p value<0.05 was considered statistically significant.
Abbreviations: CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; CAS=coronary artery stenosis ≥ 50%.

p=0.001) of the cervicocephalic arteries. However, the presence of CAS did not significantly affect the likelihood to have multi-segment (≥ 2) cervicocephalic stenosis ≥ 50% in patients with AICVD.

Then we explored the age- and sex-adjusted indicative value of CAS for having more (at least three) cervicocephalic arterial segments with stenosis ≥ 50%. All of them could be independently predicted by the presence of CAS (data not shown), where the risk of having ≥ 4 cervicocephalic arterial segments with stenosis ≥ 50% was most notably increased (adjusted OR=6.87, 95% CI: 2.90–16.29, p<0.001)

Table 3. Logistic regression analysis for the associations between CAS and CA characteristics in patients with AICVD

Characteristics	Crude OR (95%CI)	*p* value	Adjusted OR[1] (95%CI)[&]	*p* value	Adjusted OR[2] (95%CI)[§]	*p* value
CA Severity						
Presence of stenosis ≥ 50%	1.57 (0.62-4.01)	0.345	1.71 (0.53-5.53)	0.368		
Grade of the most severe stenotic segment	1.20 (0.90-1.60)	0.209	1.17 (0.82-1.65)	0.386		
CA Extent						
Presence of stenosis ≥ 50% in both sides	3.42 (1.61-7.28)	0.001*	2.94 (1.15-7.52)	0.025*	4.29 (1.67-10.98)	0.002*
Presence of stenosis ≥ 50% in both extracranial and intracranial arteries	4.70 (2.18-10.13)	<0.001*	3.10 (1.25-7.70)	0.015*	5.26 (2.24-12.35)	<0.001*
Presence of stenosis ≥ 50% in both anterior and posterior circulation	4.51 (2.11-9.64)	<0.001*	4.07 (1.57-10.58)	0.004*	5.29 (2.22-12.64)	<0.001*
Number of stenotic segments ≥ 50%	1.42 (1.20-1.68)	<0.001*	1.35 (1.10-1.64)	0.004*	1.58 (1.28-1.96)	<0.001*

*p value <0.05 was considered statistically significant.
[&]Adjusted OR[1] and 95%CI were calculated with adjustment of demographic and clinical variables whose p value <0.10 in univariate analysis (age, sex, history of coronary artery disease, systole blood pressure on admission, and glycosylated hemoglobin level).
[§]Adjusted OR[2] and 95%CI for CA extent characteristics were calculated with adjustment of the grade of the most severe stenotic segment in cervicocephalic arteries.
Abbreviations: CAS=coronary artery stenosis ≥50%; CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; OR=odds ratio; CI=confidence interval.

Table 4. Age- and sex-adjusted indicative value of CAS for CA extent characteristics in patients with AICVD

Dependent variables	Adjusted ORs of the presence of CAS	95% CIs	*P* value
Presence of stenosis ≥ 50% in both sides	3.03	1.36-6.75	0.007*
Presence of stenosis ≥ 50% in both extracranial and intracranial arteries	4.08	1.83-9.10	0.001*
Presence of stenosis ≥ 50% in both anterior and posterior circulation	4.09	1.84-9.08	0.001*
≥ two segments with stenosis ≥ 50%	2.11	0.93-4.77	0.073
≥ four segments with stenosis ≥ 50%	6.87	2.90-16.29	<0.001*

*p value <0.05 was considered statistically significant.
Abbreviations: CAS=coronary artery stenosis ≥ 50%; CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; OR=odds ratio; CI=confidence interval.

(**Table 4**).

Association between Extracranial or Intracranial CA Severity and CAS

Compared to the AICVD only group, those with concomitant CAS were more likely to have extracranial stenosis ≥ 50% and had a significantly higher grade of the most severe stenosis in extracranial arteries, while intracranial CA severity was similar between patients with AICVD with and without CAS (**Table 5**, **Fig. 2**). However, after adjusting for demographics and clinical variables, neither extracranial nor intracranial CA severity had an independent relationship with the presence of CAS (**Table 6**).

Correlation of individual Cervicocephalic Stenotic Segment ≥ 50% and CAS

After adjusting for clinical demographic variables whose p value was <0.10 in univariate analysis (age, sex, history of coronary artery disease, systolic blood pressure on admission, and glycosylated hemoglobin level), we found that CAS was differently connected

Table 5. Comparisons of extra- or intracranial CA severity between AICVD patients with and without CAS

Characteristics	Total (n=140)	AICVD + CAS (n=44)	AICVD only (n=96)	p value
Presence of extracranial stenosis ≥ 50% (n, %)	57 (40.7)	26 (59.1)	31 (32.3)	0.003*
Presence of intracranial stenosis ≥ 50% (n, %)	100 (71.4)	36 (81.8)	64 (66.7)	0.065
Grade of the most severe extracranial stenotic segment [M (Q25, Q75)]	1 (0, 3)	2 (0, 4)	1 (0, 2)	0.003*
Grade of the most severe intracranial stenotic segment [M (Q25, Q75)]	3 (1, 3)	3 (2, 3)	2 (1, 3)	0.327

*p value <0.05 was considered statistically significant.
Abbreviations: CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; CAS=coronary artery stenosis ≥ 50%.

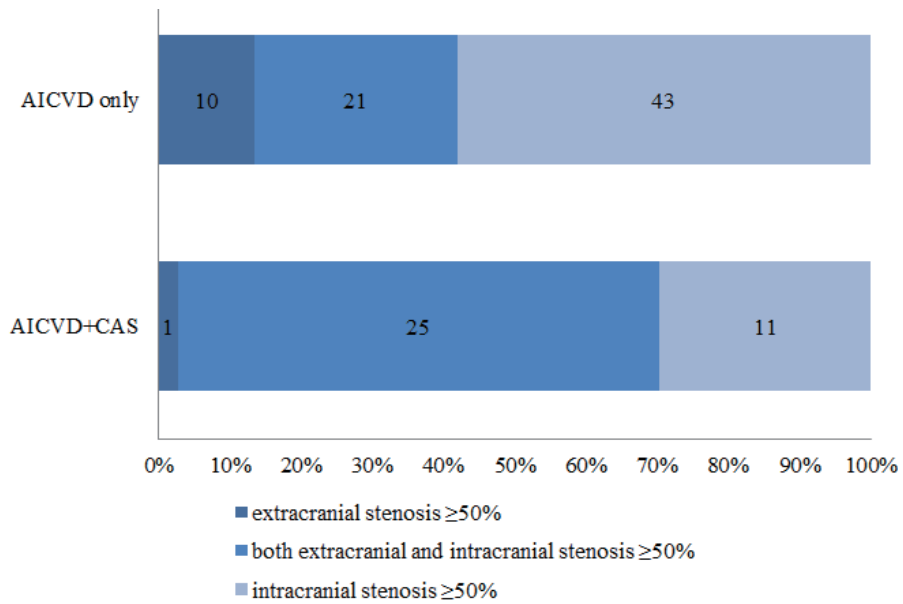

Fig. 2. Distribution of extracranial or intracranial stenosis ≥ 50% of the cervicocephalic artery in patients with AICVD with and without CAS

Abbreviations: CAS=coronary artery stenosis ≥ 50%; AICVD=acute ischemic cerebrovascular disease.

Table 6. Logistic regression analysis for the associations between CAS and extra- or intracranial CA severity in patients with AICVD

Characteristics	Crude OR (95%CI)	p value	Adjusted OR (95%CI)§	p value
Presence of extracranial stenosis ≥ 50%	3.03 (1.45-6.33)	0.003*	2.18 (0.91-5.22)	0.081
Presence of intracranial stenosis ≥ 50%	2.25 (0.94-5.40)	0.070	2.34 (0.77-7.11)	0.134
Grade of the most severe extracranial stenotic segment	1.48 (1.16-1.90)	0.002*	1.31 (0.98-1.75)	0.071
Grade of the most severe intracranial stenotic segment	1.18 (0.90-1.53)	0.229	1.16 (0.83-1.61)	0.384

*p value <0.05 was considered statistically significant.
§Adjusted OR and 95%CI were calculated with adjustment of demographic and clinical variables whose p value <0.10 in univariate analysis (age, sex, history of coronary artery disease, systole blood pressure on admission, and glycosylated hemoglobin level).
Abbreviations: CAS=coronary artery stenosis ≥ 50%; CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; OR=odds ratio; CI=confidence interval.

Table 7. Association between CAS and stenosis ≥ 50% of different cervicocephalic arterial segment in patients with AICVD

Cervicocephalic arterial segment	AICVD + CAS (n=44) [&]	AICVD only (n=96) [&]	p value	Adjusted OR (95%CI) [§]	p value
Extracranial segments					
Common carotid arteries	13 (29.5)	6 (6.3)	<0.001*	4.52 (1.24-16.51)	0.023*
Extracranial carotid arteries	16 (36.4)	13 (13.5)	0.002*	2.76 (1.01-7.52)	0.047*
Extracranial vertebral arteries	17 (38.6)	16 (16.7)	0.004*	2.16 (0.82-5.66)	0.119
Proximal intracranial segments					
Intracranial carotid arteries	16 (36.4)	13 (13.5)	0.002*	3.72 (1.37-10.11)	0.010*
Intracranial vertebrobasilar arteries	24 (54.5)	22 (22.9)	<0.001*	2.86 (1.11-7.35)	0.029*
Distal intracranial segments					
Anterior cerebral arteries	6 (13.6)	11 (11.5)	0.714	1.05 (0.31-3.64)	0.933
Middle cerebral arteries	17 (38.6)	34 (35.4)	0.713	1.41 (0.59-3.39)	0.443
Posterior cerebral arteries	23 (52.3)	25 (26.0)	0.002*	2.65 (1.07-6.55)	0.035*

*p value <0.05 was considered statistically significant.
[&]Comparisons of stenosis ≥ 50% of different cervicocephalic arterial segment between AICVD patients with and without CAS were displayed .61acranial carotidrteries as number (%)
[§]Adjusted OR and 95%CI were calculated with adjustment of demographic and clinical variables whose p value <0.10 in univariate analysis (age, sex, history of coronary artery disease, systole blood pressure on admission, and glycosylated hemoglobin level).

with stenosis ≥ 50% of each cervicocephalic arterial segment in patients with AICVD. For the extracranial stenosis ≥ 50%, those in the anterior circulation (common carotid, extracranial carotid arteries) rather than those in the posterior circulation (extracranial vertebral arteries) were related to CAS. For the proximal intracranial stenosis ≥ 50%, both those in the anterior and posterior circulation (intracranial carotid, intracranial vertebrobasilar arteries) were independent indicators of CAS. For the distal intracranial stenosis ≥ 50%, those in the posterior circulation (posterior cerebral arteries) instead of those in the anterior circulation (anterior cerebral, middle cerebral arteries) were associated with CAS (**Table 7**).

Severity and Extent of CA in Patients with AICVD with Symptomatic and Asymptomatic CAS

Among 44 patients with both AICVD and CAS, 15 (34.1%) patients were positive for a history of coronary artery disease, while the remaining 29 patients had no cardiac symptoms. Counterintuitively, in comparison to patients with AICVD with asymptomatic CAS, those with symptomatic CAS were inclined to have a smaller number of stenotic segments ≥ 50% (interquartile range 0–6 vs. 1.5–6.5, p=0.004) and a lower grade of the most severe stenotic segment in cervicocephalic arteries (interquartile range 1–4 vs. 3–4, p=0.003). Moreover, the prevalence of cervicocephalic arterial stenosis ≥ 50%, as well as the likelihood of having stenosis ≥ 50% in both sides and in both anterior and posterior circulation of the cervicocephalic arteries, was numerically larger in patients with AICVD with asymptomatic CAS (**Table 8**).

Discussion

In this cross-sectional CTA study of patients with AICVD, CA was assessed comprehensively from aspects of both severity and extent, and coronary atherosclerosis was evaluated simultaneously. We found that if CAS coexisted, the patients with AICVD distinctively tended to have more diffused stenosis in the cervicocephalic vasculature, and the extent of CA was profiled in a more multifaceted manner than that reported in the literature[4, 5]. Meanwhile, the CA severity was not significantly different between patients with AICVD with and without CAS.

Both symptomatic and asymptomatic CAS were indicators of high vascular risk for patients with AICVD[7]. This study was designed to portray CA characteristics in patients with AICVD and CAS together, laying the foundation for their prognostic judgment and clinical management. Therefore, we evaluated the coronary arteries of all appropriate patients with AICVD, regardless of their cardiac symptoms. To our knowledge, only Amarenco *et al.*[6] had reported the relationship between coronary atherosclerosis and CA in AICVD without the exclusion of patients who had prior cardiac symptoms. However, they assessed only the severity of extracranial carotid arteries by ultrasound to reflect CA, and patients with a history of coronary artery disease (acute coronary syndrome, myocardial infarction, or previous coronary revascularization) were grouped as

Table 8. Comparisons of CA characteristics between AICVD patients with symptomatic and asymptomatic CAS

Characteristics	AICVD with symptomatic CAS (n=15)	AICVD with asymptomatic CAS (n=29)	p value
CA Severity			
Presence of stenosis ≥ 50% (n, %)	11 (73.3)	26 (89.7)	0.171
Grade of the most severe stenotic segment [M (Q25, Q75)]	3 (1, 4)	3 (3, 4)	0.003*
CA Extent			
Presence of stenosis ≥ 50% in both sides (n, %)	10 (66.7)	20 (69.0)	0.877
Presence of stenosis ≥ 50% in both extracranial and intracranial arteries (n, %)	9 (60.0)	16 (55.2)	0.759
Presence of stenosis ≥ 50% in both anterior and posterior circulation (n, %)	7 (46.7)	20 (69.0)	0.150
Number of stenotic segments ≥ 50% [n, M (Q25, Q75)]	4 (0, 6)	4 (1.5, 6.5)	0.004*

*p value <0.05 was considered statistically significant.
Abbreviations: CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; CAS=coronary artery stenosis ≥ 50%.

"coronary stenosis ≥ 50%" without coronary angiogram evaluation in their analysis. Notably, "positive coronary artery disease history" did not necessarily mean "coronary stenosis ≥ 50%." As shown in our study, 7/51 (13.7%) patients with previous coronary artery disease had coronary stenosis <50% on CTA.

Most prior studies focused on the CA severity features in patients with AICVD with CAS[6, 10, 11]. The Predicting Asymptomatic Coronary Artery Disease in Patients With Ischemic Stroke and TIA (PRECORIS) study demonstrated that the severity of atherosclerosis in cervicocephalic arteries was independently associated with the prevalence of asymptomatic CAS in patients with AICVD (adjusted OR=2.3 for stenosis <50% and 3.7 for stenosis ≥ 50%)[4] and developed a predictive score based on these findings[10]. In our study, however, it seemed that CA severity characteristics had no significant relationship with coexisting CAS in patients with AICVD. Similar results were obtained when we performed the analysis only in patients with AICVD without a history of coronary artery disease. The discrepancy may be attributed to the generally serious CA in our study subjects. Of our patients, 90.0% had cervicocephalic atherosclerotic stenosis of any grade, while 79.3% had stenosis ≥ 50%. By contrast, these two ratios were 40% and 28%, respectively, in the PRECORIS study[4]. Apart from racial differences (European vs. Asian), the relatively low prevalence of cervicocephalic atherosclerotic stenosis in the PRECORIS study might also because they excluded patients with AICVD with a modified Rankin scale score ≥ 3, and who possibly have more severe CA.

On the other hand, as the association between CAS with extracranial stenosis had been suggested to be stronger than that of CAS with intracranial stenosis[11, 22], we further respectively assessed the relationship of CAS with extracranial or intracranial CA severity characteristics. According to our data, although extracranial CA severity was more associated with CAS in comparison to intracranial CA severity in the univariate analysis, neither of them had a correlation with CAS independent of clinical demographic characteristics. Further, as demonstrated in **Fig. 2**, the potentially stronger association between CAS and extracranial CA severity was possibly because patients with AICVD with extracranial stenosis ≥ 50% were more likely to have concurrent extracranial and intracranial stenosis ≥ 50% than those with intracranial stenosis ≥ 50% (46/57 vs. 46/79). Thus, the presence of extracranial stenosis ≥ 50% might actually reflect a higher likelihood of patients with AICVD having diffused CA, which was an independent marker of CAS in our study.

Some prior researchers further explored the relationship between CAS and stenosis ≥ 50% in different segments of the cervicocephalic arteries. Arenillas *et al.*[23] found that intracranial carotid artery stenosis and symptomatic vertebrobasilar stenosis, rather than stenosis in the middle cerebral and posterior arteries, were independently associated with silent myocardial ischemia among patients with symptomatic intracranial atherosclerosis. Yoo *et al.*[5] observed that stenosis ≥ 50% of the carotid, vertebral, and basilar arteries had a closer relationship with asymptomatic CAS in patients with AICVD than that of the anterior, middle and posterior cerebral arteries. However, cerebral angiography was largely performed with magnetic resonance angiography in these two studies (88% and 66.5%, respectively). In our research, CA of all the patients was assessed with CTA, providing a more accurate evaluation of the atherosclerotic lesions, especially those located in the original parts of the vertebral arteries, than MRA[24, 25]. We found that the prox-

imal–distal and anterior–posterior location of stenosis ≥ 50% in the cervicocephalic arteries could exert significant impacts on their correlations with the presence of CAS in patients with AICVD. Therefore, the associations between CAS and cervicocephalic stenosis ≥ 50% might be present in some, but not all extracranial or intracranial arteries. This can be explained by the anatomic and physiological differences between distinct cervicocephalic arterial segments, but the definite reasons are still unknown.

Atherosclerosis is a systemic disease; theoretically, the coexistence of coronary atherosclerosis in patients with AICVD may indicate more diffused atherosclerotic lesions in the cervicocephalic vasculature. There was only preliminary research on this relationship. In a study of patients with symptomatic carotid stenosis, bilateral carotid disease was more associated with previous myocardial infarction compared to purely unilateral disease (adjusted OR=1.7)[26]. Our results further manifested that bilateral cervicocephalic arterial stenosis ≥ 50% and the presence of CAS were mutually indicative in patients with AICVD.

Measuring the CA extent from another point of view, Yoo *et al.*[5] found that multi-segment (≥ 2) cervicocephalic stenosis ≥ 50% was independently related to asymptomatic CAS in patients with AICVD (adjusted OR=1.8). But in our study, the risk of having multi-segment (≥ 2) cervicocephalic stenosis ≥ 50% was not increased significantly with the presence of CAS, even if patients with AICVD with cardiac symptoms were excluded from the analysis. We found that patients with both AICVD and CAS tended to have a larger number of ≥ 50% stenotic segments in the cervicocephalic arteries, but the coexistence of CAS only increased the likelihood of having three or more cervicocephalic arterial segments with stenosis ≥ 50%. Thus, the distinct results with previous research might also be explained by the generally serious CA in our study. Indeed, multi-segment (≥ 2) cervicocephalic stenosis ≥ 50% was presented in 58.6% of our patients with AICVD, versus 27.7% in Yoo *et al.*'s study[5].

Furthermore, our study showed that patients with AICVD with CAS were more likely to have stenosis ≥ 50% in both extracranial and intracranial cervicocephalic arteries, as well as in both anterior and posterior circulation. They perhaps represented a higher degree of diffused atherosclerosis than multi-segment (≥ 2) cervicocephalic stenosis ≥ 50%, serving as more sensitive CA extent markers for the coexistence of CAS in patients with AICVD, which has not been investigated before.

Why did our data manifest that CA extent but not CA severity was related to CAS in patients with AICVD? On one hand, the coexistence of AICVD and CAS might suggest an advanced and generalized atherosclerotic status; thus, it would be appropriate to use indices reflecting more serious atherosclerotic conditions to portray the characteristics of CA in examining their connections with CAS among patients with AICVD. Meanwhile, mild atherosclerotic lesions might exist in most patients with AICVD, being less discriminative between those with and without CAS. In our study, the characteristics of CA extent essentially represented diffused stenosis ≥ 50%, which were more serious than the mere presence of stenosis ≥ 50% (one characteristic of CA severity). Given that the severity and extent of CA in this study population was generally serious, perhaps only diffused cervicocephalic stenosis ≥ 50% could reach the threshold to distinguish those with and without CAS. On the other hand, we found that stenosis ≥ 50% in each cervicocephalic arterial segment was differentially associated with CAS; thus, the most severe stenotic segment might not be the most related to CAS, and the grade of the most severe stenotic segment (another characteristic of CA severity) might not parallel the possibilities of having CAS. In contrast, the characteristics of CA extent could combine atherosclerotic information from multiple segments and mitigate the differences between each segment, becoming more associated with the presence of CAS.

Notwithstanding that only the extent but not the severity of CA was related to CAS in patients with AICVD in this study, we believed that both CA severity and CA extent were important perspectives to delineate the association between coronary atherosclerosis and CA in patients with AICVD, while the statistical significance of their correlations with CAS might differ in distinct study populations and in various stages of systemic atherosclerosis. Previously, the extent of CA was less evaluated than its severity; our work aided in offering a more integrated picture of the relationship of CA with CAS in patients with AICVD.

In addition, no study had compared the CA characteristics between patients with AICVD with symptomatic and asymptomatic CAS. We performed this analysis, but the test power was low due to the small number of patients in each subgroup. Interestingly, our data implied that patients with AICVD with asymptomatic CAS might have even more serious CA than those with symptomatic CAS. It is likely that the treatment for previous coronary artery disease had systemically ameliorated the progression of CA. Nevertheless, this observation needs to be verified by larger-scale studies and the underlying mechanism should be further probed.

Altogether, our study suggested an independent relationship of CA extent with CAS in patients with

AICVD. Just observing the CA severity could not sufficiently distinguish patients with AICVD with CAS from those without, as most patients with AICVD had severe CA. But patients with CAS might have significantly more diffused CA.

The CA extent characteristics, including stenosis ≥ 50% in both sides, both extracranial and intracranial, both anterior and posterior circulation, as well as the number of stenotic segments ≥ 50% in the cervicocephalic arteries, have been shown to be interconnected with unfavorable functional recovery, stroke/TIA recurrence, and combined vascular ischemic events in patients with AICVD[12, 13]. Cohort studies should be designed to test whether diffused CA is one of the underlying mechanisms for the poor outcomes in patients with both AICVD and CAS[7, 8, 27, 28]. Further research is needed on the utility of the close relationship between diffused CA and CAS in optimizing the risk stratification and clinical management of AICVD.

There are several limitations to this study. First, all the study subjects were enrolled from a single senior stroke unit. The sample size was not large, males were predominant, and CA was generally serious in both severity and extent. Caution must be taken in the generalizability of our results. Second, CTA is not the gold standard diagnostic tool to detect arterial stenosis, although it is one of the most accurate noninvasive angiography methods, and the CTA technology used in this study can feasibly and safely examine the coronary and cervicocephalic arteries at the same time. Third, some arterial stenosis in this study might not be atherosclerotic, but caused by other pathologies, although we carefully searched for other possible reasons for cervicocephalic arterial stenosis and excluded the suspected patients.

Conclusion

Patients with AICVD with CAS tended to have more diffused CA than those without CAS, although they might have equally severe cervicocephalic arterial stenosis. The CA extent correlated with CAS in patients with AICVD, regardless of CA severity. A comprehensive evaluation of CA from aspects of both extent and severity is important to reveal and further utilize the associations between coronary atherosclerosis and CA in patients with AICVD.

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Conflict of Interest

None.

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Supplemental Table 1. Logistic regression analysis for the associations between CAS and CA characteristics in AICVD patients with additional control of ACIVD subtype

Characteristics	Adjusted OR (95%CI) [§]	*p* value
CA Severity		
Presence of stenosis ≥ 50%	1.55 (0.44-5.48)	0.497
Grade of the most severe stenotic segment	1.12 (0.77-1.64)	0.561
CA Extent		
Presence of stenosis ≥ 50% in both sides	2.69 (1.01-7.18)	0.048*
Presence of stenosis ≥ 50% in both extracranial and intracranial arteries	2.94 (1.14-7.57)	0.026*
Presence of stenosis ≥ 50% in both anterior and posterior circulation	3.80 (1.39-10.39)	0.009*
Number of stenotic segments ≥ 50%	1.33 (1.08-1.64)	0.009*

*p value <0.05 was considered statistically significant.
[§]Adjusted OR and 95%CI were calculated with adjustment of demographic and clinical variables whose p value <0.10 in univariate analysis (age, sex, history of coronary artery disease, systole blood pressure on admission, and glycosylated hemoglobin level) and AICVD subtype. Abbreviations: CAS=coronary artery stenosis ≥ 50%; CA=cervicocephalic atherosclerosis; AICVD=acute ischemic cerebrovascular disease; OR=odds ratio; CI=confidence interval.