Significant Contribution of Aortogenic Mechanism in Ischemic Stroke
Observation of Aortic Plaque Rupture by Angioscopy

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ABSTRACT

BACKGROUND Although embolic stroke accounts for most cerebral infarction, examinations to identify the embolic source have been insufficient. Nonobstructive general angioscopy (NOGA) has developed to allow the detailed observation of atheromatous changes of the aorta.

OBJECTIVES The purpose of this study was to clarify the importance of the aortogenic mechanism in the development of ischemic stroke.

METHODS We examined 114 consecutive patients whose aorta was observed by NOGA and who subsequently underwent brain magnetic resonance imaging to detect ischemic stroke lesions. In the evaluation of the aorta, the presence and location of spontaneously ruptured aortic plaque (SRAP) were determined. The aorta was observed from the origin to the arch (proximal aorta [PAo]) and the proximal descending aorta.

RESULTS Forty-nine of 114 patients had SRAP observed by NOGA. Among these, 24 had SRAP in the PAo, and 43 had SRAP in the descending aorta. Thirty-three patients had ischemic stroke lesions, including 6 with a clinical neurologic deficit. The frequency at which SRAP was detected in these patients was significantly higher in comparison to 81 patients without ischemic stroke (69% vs 33%; P < 0.01). The sensitivity and specificity of the presence of SRAP for ischemic stroke were 0.70 and 0.68, respectively. The presence of SRAP in PAo was significantly correlated with ischemic stroke (odds ratio: 14.3; P < 0.001).

CONCLUSIONS In the treatment of ischemic stroke, attention should be paid to SRAP, especially that in the PAo. (STROKE-NOGA [Spontaneously Ruptured aOrtic plaques as a potential cause of embolic stroKes visualized by Non-Obstructive General Angioscopy] Study; UMIN000034588) (JACC: Asia 2022;2:750–759) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ischemic stroke is one of the major causes of mortality, long-term disability, and the development of cognitive disorder.1 Most ischemic strokes, including cortical infarcts, subcortical small infarcts, and lacunar infarcts, are caused by an embolic mechanism, regardless of their source.2–4 However, the cause of ischemic stroke remains uncertain in approximately 25% of cases, despite the complete evaluation of embolic sources; this is referred to as cryptogenic stroke.2 Most cryptogenic ischemic strokes have embolic features, suggesting a possible cardiogenic or aortogenic origin.3 Subclinical covert atrial...
fibrillation (AF) is considered a potent candidate for cryptogenic strokes. Long-term cardiac monitoring revealed that covert AF was present in 12% of patients with cryptogenic stroke. Two studies were conducted to verify whether direct oral anticoagulant (DOAC) treatment could prevent the recurrence of ischemic stroke of undetermined source. Two DOAC agents (rivaroxaban and dabigatran) were not superior to aspirin in preventing recurrent stroke. This suggested that embolism of not only cardiogenic (mainly caused by AF) but also aortogenic origins should be considered as a major cause of embolic stroke. Some studies reported that complex aortic plaques, which show ulcer-like morphology, with characteristics of rupture, and which contain thrombi, are considered an embolic source for ischemic stroke. \[\text{AF} \rightarrow \text{AF embolism} \rightarrow \text{Brain} \]

Recently, nonobstructive general angioscopy (NOGA) has been used to observe large arteries, including the aorta, without blocking the blood flow. It is reported that ≥20% of patients with coronary artery disease had spontaneously ruptured aortic plaque (SRAP) in the arch and proximal descending aorta (DAo). Observation by NOGA can record dynamic images of SRAP, which show the constant liberation of debris, including atheromatous materials, thrombus, and cholesterol crystals into the blood. Embolic events attributed to the SRAP should be considered in the clinical setting for conditions such as critical limb ischemia and cryptogenic ischemic stroke.

Previous studies investigating the association between aortic plaque and ischemic stroke used transesophageal echocardiography (TEE) or magnetic resonance imaging (MRI) to detect aortic plaque. In comparison to these modalities, NOGA has high spatial resolution. Thus, NOGA may be useful for identifying the source of ischemic stroke. This study aimed to investigate the relationship between SRAP detected by NOGA and ischemic stroke lesions.

**METHODS**

**STUDY POPULATION AND DESIGN.** From January 2018 to December 2019, consecutive patients who were scheduled for angioscopy of the aorta following coronary angiography for coronary artery disease were eligible for enrollment in this study. Patients who gave their consent for inclusion in the study underwent aortic angioscopy by NOGA, and subsequent brain magnetic resonance imaging (MRI) was performed within 3 months after catheterization. Ischemic stroke was defined as a disease with cerebral infarct lesions on brain MRI, regardless of the presence or absence of neurologic symptoms. The exclusion criteria were as follows: 1) patients who were ineligible for MRI examination because of internal metal, claustrophobia, or other factors; 2) patients with acute cerebral infarction within 72 hours before and after catheterization; 3) patients with chronically persistent AF; 4) patients with paroxysmal AF documented when staying in the hospital or visiting an outpatient clinic; and 5) patients demonstrating lesions with ≥50% lumen stenosis in either the intracranial or carotid arteries as detected by magnetic resonance angiography (MRA). (These patients were treated either in medically or surgically by a neurologist.) Written informed consent was obtained from all study patients. This study was approved by the ethical committee of Osaka Police Hospital and registered in the University Medical Information Network Clinical Trials Registry (STROKE-NOGA [Spontaneously Ruptured aOrtic plaques as a potential cause of embolic stroKEs visualized by Non-Obstructive General Angioscopy]; UMIN000034588).

**OBSERVATION OF THE AORTA BY NOGA.** A 6-F Ikari-left 3.5 guiding catheter (Heartrail II, Terumo) was used to perform an angioscopic examination via a left radial artery approach. The angioscopy system consisted of an image fiberscope (VISIBLE, Fiber Tech Co. Ltd.) and a console (Intercet Medical Co. Ltd.). Angioscopic images were obtained by infusion of low-molecular dextran from the tips of the guiding and probing catheters to clear off red blood cells in front of the tip lens of the image fiberscope. Observation of the aorta by NOGA has been described previously. Briefly, an image fiberscope was set in a 4-F probing catheter, and these were pulled back together with a guiding catheter along the aorta to observe the inner surface of the aorta. Initially, these catheters were pulled back from the ascending aorta to the left subclavian artery. Then, both the image fiberscope and 4-F probing catheter were pulled out. Next, a 6-F guiding catheter was introduced into the abdominal aorta, and both the image fiberscope and 4-F probing catheter were inserted in the 6-F guiding catheter. These catheters were pulled back from the abdominal aorta to the left subclavian artery. Images were recorded on a hard disk for offline analysis.

Aortic plaque was defined as visible atherosclerosis on the inner surface of the aorta by NOGA. The evaluation of aortic plaques by NOGA has
been described previously. This includes ruptured plaque with a “puff-like” appearance and/or a “chandelier-like” appearance. “Puff” rupture is defined as a ruptured plaque with white or white-yellow puff-like materials that easily blow out spontaneously, whereas “chandelier” rupture is defined as a ruptured plaque with materials that glisten in the light from the tip of the NOGA fiber catheter. These plaques constantly liberate debris including thrombi, atheromatous materials, and cholesterol crystals into the blood and are referred to as SRAPs.

Observation by NOGA can be used to diagnose the dynamic morphology of aortic plaques in real time. It is possible to observe and diagnose the constant liberation of debris including thrombi, atheromatous materials, and cholesterol crystals into the blood from SRAP.

The presence of complex plaques in the DAo has been recognized as a potential mechanism of embolic stroke. Therefore, the observation range was defined as from the ascending aorta to the DAo. The ascending aorta and arch were defined as the proximal aorta (PAo), which ranges from the origin of the aorta to the left subclavian artery. The segment from the left subclavian artery to the height of the fifth thoracic vertebra was defined as the DAo. The outcome of aortic observation by NOGA was defined as the presence and location of SRAPs.

**BRAIN MRI.** Within 3 months after observation of the aorta by NOGA, a brain MRI examination was conducted.
performed to evaluate ischemic stroke lesions using a 1.5-T MRI system (Signa EXCITE HDxt 1.5T, GE Healthcare). The carotid artery and intracranial artery were evaluated by simultaneous magnetic resonance angiography (MRA). The whole brain was scanned at a slice thickness of 5 mm with an interslice gap of 1.5 mm. Conventional MRI sequences, such as T1-weighted imaging, T2-weighted imaging, and fluid attenuated inversion recovery (FLAIR) were examined. The repetition times of these sequences were 500; 4,000, and 9,000 ms, respectively. The times to echo of these sequences were 14, 90, and 114 ms, respectively. We also examined diffusion-weighted imaging (DWI) to detect acute stroke. After differentiating acute stroke, we assessed chronic stroke. A chronic stroke lesion was defined as a lesion of ≥3 mm in size with a signal intensity level consistent with cerebrospinal fluid on all sequences (ie, low intensity on T1-weighted imaging, high intensity on T2-weighted imaging, and low [null] intensity on FLAIR imaging). An ischemic stroke lesion in the subcortical region was defined as a lesion for which the center showed null intensity, with a hyperintense rim on FLAIR imaging.19 Silent brain infarction was defined as a stroke without a clinically apparent neurologic deficit.

**Statistical Analyses.** Analyses were conducted using SPSS 25.0 for Windows (SPSS Incorporation). Quantitative variables were expressed as the mean ± SD.

A binary logistic regression analysis was performed to explore the association between patient-side variables and the existence of ischemic stroke. The patient-side variables include male sex, older age (>70 years), hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, and the existence of SRAP in the PAo or DAo. These variables were entered in a single step for the analysis. Hypertension was defined as blood pressure of ≥140/90 mm Hg or the use of antihypertensive drugs. Dyslipidemia was defined as serum low-density lipoprotein cholesterol level of ≥140 mg/dL or treatment with medication. Diabetes mellitus was defined as serum glycosylated hemoglobin level of ≥6.2% or treatment with medication. Chronic kidney disease was defined as estimated glomerular filtration rate of <60 mL/min/1.73 m².

**Results**

**Study Population and Patient Characteristics.** During the study period, 199 patients underwent coronary angiography and coronary angiography. Among those, 123 provided their consent for inclusion in the study and underwent aortic angioscopy. These patients underwent brain MRI within 3 months after catheterization. Five patients were excluded because of paroxysmal AF detected by electrocardiography monitoring during the hospital stay or in an electrophysiology examination in the outpatient clinic. Four patients with carotid or intracranial artery disease detected by brain MRA who were treated by neurosurgery were also excluded. Finally, 114 patients were included in this study. The durations from NOGA to MRI were recorded in a histogram (Supplemental Figure 1). Brain MRI was performed an average of 1.5 ± 1.2 months after NOGA.

**Frequency of SRAP.** In all cases, NOGA observation of the aorta could be performed, and images sufficient for an analysis were obtained. A representative image of SRAP observed by NOGA is shown in Figure 1. The movie recorded around the arch (Video 1) shows the dynamic observation of spontaneous plaque rupture. There were 24 (21%) cases of SRAP in the PAo, and 43 (38%) cases of SRAP in the DAo. There were 49 (43%) cases of SRAP in the observation area from the PAo to DAo (Figure 2). The patient characteristics are shown in Table 1. When patients with and without SRAP were compared, those with SRAP are significantly older than those without SRAP (P < 0.001).

**Frequency of Ischemic Stroke.** Ischemic stroke lesions were found in 33 cases (29% of all subjects). No lesions demonstrated high intensity on DWI imaging, suggesting that all ischemic stroke lesions investigated were chronic-phase stroke. Among
these, lesions in the cerebral cortex were found in 4 cases and in the subcortical white matter in 31 cases; there were 2 cases involving coexistent lesions. Cerebellar infarct lesions were found in 4 cases, and pontine infarct lesions were found in 3 cases.

Silent brain infarction, characterized by a lack of clinically apparent neurological deficit, accounted for 27 (82%) of the total cases of ischemic stroke. Symptomatic brain infarction, characterized by a lack of clinically apparent neurological deficit, accounted for 27 (82%) of the total cases of ischemic stroke. Symptomatic brain infarction was found in 6 patients (motor paralysis, n = 2; dysarthria, n = 3; and aphasia n = 1). The characteristics and medication history of these 6 patients are shown in Supplemental Table 1.

Figure 3 shows a representative case of ischemic stroke, and a movie recorded at the aortic arch is shown in Video 2. The patient in this case developed ischemic stroke with symptoms of dysarthria and weakness of the right upper limb. In this case, the NOGA examination was performed 30 days after the onset of ischemic stroke, and brain MRI was performed 69 days after the onset (Figure 3). The MRI and MRA images at the onset of stroke are shown in Supplemental Figure 2. The absence of a history of atrial fibrillation and absence of lesions in the carotid and intracranial arteries suggests the possibility of aortogenic stroke.

RELATIONSHIP BETWEEN SRAP AND ISCHEMIC STROKE. The frequency of SRAP observed by NOGA in patients with ischemic stroke is shown in Figure 4. In comparison to patients without ischemic stroke, patients with ischemic stroke were significantly more likely to have SRAP (69% vs 33%; P < 0.01). In 23 (69%) cases of ischemic stroke, SRAP was found in the range from the PAo to DAO.

Next, we investigated the relationship between the presence or absence of SRAP and the occurrence of
ischemic stroke (Figure 5). Ischemic stroke lesions were found in 23 of 49 patients with SRAP detected by NOGA. The sensitivity and specificity of the presence of SRAP for ischemic stroke were 0.70 and 0.68, respectively. In the PAo region, ischemic stroke lesions were found in 18 of 24 patients. The sensitivity and specificity of SRAP for PAo to ischemic stroke were 0.55 and 0.93, respectively. The positive predictive value of the presence of SRAP in PAo for ischemic stroke was 0.75. In the DAo region, ischemic stroke lesions were found in 19 of 43 patients with SRAP in the DAo. The sensitivity and specificity of
SRAP in the DAO for ischemic stroke were 0.58 and 0.70, respectively.

A logistic regression analysis revealed that the presence of SRAP in the PAO was significantly correlated with ischemic stroke, with an odds ratio of 14.3 (Table 2). Next, the relationship between each factor and silent ischemic stroke was investigated. Twenty-seven patients, excluding 6 with symptomatic cerebral infarction, were silent stroke patients. A similar regression analysis was performed on patients with silent ischemic stroke. The same was true for the results of the logistic regression analysis of 27 cases of silent ischemic stroke. The presence of SRAP in the PAO was significantly correlated with silent ischemic stroke, with an odds ratio of 17.3 (Table 3).

**Discussion**

In the present study, we observed aortic plaques and their dynamic morphology by NOGA in patients with coronary artery disease, and brain MRI was performed within 3 months after cardiac catheterization. The sensitivity and specificity of SRAP detected by NOGA for the presence of ischemic stroke were 0.68 and 0.70, respectively. Furthermore, SRAP in the PAO had a positive predictive value of 0.75 for ischemic stroke and was correlated with the occurrence of ischemic stroke, with an odds ratio of 14.3. Studies of aortic atherosclerosis using NOGA have reported that SRAP can cause embolism in various organs.12,13,15,17,18 This study showed that SRAP—especially in the ascending aorta and arch region—can be a major cause of ischemic stroke, including cortical or subcortical infarction (Central Illustration).

AF is recognized as one of the major causes of embolic stroke.2 A systematic review reported that AF was detected in approximately 24% of individuals after stroke or transient ischemic attack.20 In this study, SRAP was present in approximately 70% of patients with ischemic stroke. This study showed that SRAP was frequently observed in patients with ischemic stroke without AF. Previous studies predicted that patients with AF who have not received anticoagulant therapy develop ischemic stroke at a rate of 5% per year.21 In this study, we revealed a very strong association between the presence of SRAP and ischemic stroke. The subjects of this study were patients with coronary artery disease. Therefore, the patient backgrounds and characteristics differ from those of earlier studies. These findings urge physicians to focus not only on AF but also on aortic plaques when treating patients with embolic stroke, especially patients who have coronary artery disease.

In this study population, 28% of subjects had ischemic stroke lesions. Subcortical white matter infarctions accounted for a large proportion, with relatively small lesions. Previous studies have suggested that, in many cases, the causes of stroke can be attributed to an embolic mechanism.2 Lacunar stroke, which occurs in the subcortical white matter, is classified into cerebral small vessel disease, and hypertension is considered to be greatly involved in the mechanism of lacunar stroke.4,22 On the other hand, some studies suggest that many lacunar strokes are caused by an embolic mechanism.22,23 It is known that the cause of aortogenic stroke is not limited to small emboli.1 Therefore, it is not possible to differentiate between aortogenic stroke and cardiogenic stroke based on the size of the particle alone. However, it is quite possible that small embolic particles released from SRAP will occlude cerebral perforator arteries (Central Illustration).

In the present study, logistic regression indicated that hypertension was not strongly related to ischemic stroke. Because all patients included in this study had coronary artery disease, they were already taking medications for atherosclerosis, including antihypertensive drugs. This clinical setting may have diminished the impact of hypertension on the occurrence of small infarctions. In the present study,
many of the infarct lesions found on brain MRI were small, suggesting the involvement of microembolic particles. The small size of embolic particles does not necessarily suggest that the cause of the stroke is aortogenic. However, NOGA can observe the region around the aortic arch in detail. NOGA can dynamically observe thrombi and plaque debris released from SRAP.\textsuperscript{13} Because the spatial resolution of NOGA is very high, it is possible to identify microembolic particles liberated from SRAP.\textsuperscript{13} This suggests that microembolic particles liberated from SRAP are a promising candidate as the cause of the ischemic strokes investigated in this study.

Most of the ischemic strokes investigated in this study were silent brain infarctions. Twenty-seven of the 114 patients (24%) studied had silent brain infarctions. In general, silent brain infarctions are found in 10% to 20% of the whole population.\textsuperscript{24} Because all subjects of this study were patients with coronary artery disease who had risk factors for
atherosclerosis, patients in this study may have had silent brain infarctions at a higher rate than the general population.

Some studies reported that silent brain infarction has a strong correlation with the future onset of dementia, symptomatic stroke, and deterioration of the life prognosis. It has been reported that AF is involved in the development of silent brain infarction. On the other hand, plaque in the aortic arch detected by TEE has been reported to be associated with silent brain infarction. The present study demonstrated that SRAP in the PAo is a more strongly related factor in comparison to other inducers of atherosclerosis, although patients with AF were excluded from this study. Even in silent brain infarction, attention should be focused on aortogenic stroke caused by SRAP.

STUDY LIMITATIONS. The present study was associated with several limitations. First, this study was conducted in a single institute, and the number of subjects was relatively small. Second, this study did not perform a complete examination to detect covert paroxysmal AF and search for thrombus. Of the 123 patients who gave their consent to participate in this study, 5 had paroxysmal AF documented before brain MRI. However, the possibility that there were more patients with covert paroxysmal AF cannot be ruled out because it is difficult to detect this arrhythmia by ordinary electrocardiography. Implantable cardiac monitoring is required to detect covert AF, but this was not performed in our study. One of the possible sources of thromboembolism includes paradoxical embolism caused by patent foramen ovale. TEE is required to detect patent foramen ovale, but only a small number of patients in this study underwent TEE. The 2 mechanisms of embolic stroke involve intra-atrial or venous thrombosis. Considering that DOAC agents could not show superiority to aspirin in the prevention of recurrent stroke, we believe that the conclusion of this study—that attention should be focused on aortogenic stroke—remains unchanged. Third, we did not perform baseline brain MRI before NOGA. It is difficult to determine whether the identification of cerebral infarct lesions on MRI existed before the observation of NOGA. The safety of NOGA has been established, and no embolic complications have been reported in previous studies. It is difficult to assume that iatrogenic cerebral infarction will occur. Fourth, pathologic changes with mild stenosis or plaques in the intracranial or carotid arteries may cause stroke events as they do with severe stenosis. In this study, all MRI scans included MRA of the intracranial and carotid arteries, and patients who received treatment for stenotic lesions ≥50% in diameter were excluded from the present study. Because of the spatial resolution of MRA, the possibility that mild lesions in the intracranial or carotid arteries were the cause of ischemic strokes remains. Finally, NOGA may have limited ability to detect SRAP completely. Although NOGA can observe the entire aorta with high probability, there may be cases where SRAPs are missed because of anatomic problems of the aortic structure.

CONCLUSIONS

There was a significant correlation between ischemic stroke and SRAP in patients with coronary artery disease. In particular, SRAP in the PAo was strongly associated with silent brain infarction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the treatment of brain infarction, the aortogenic mechanism of ischemic stroke may be of greater importance than has previously been recognized in the clinical setting. Angioscopic observation of the aorta can provide detailed information on the characteristics of plaque morphology and dynamics of plaque disruption. In particular, spontaneously ruptured plaque in the proximal region of aorta is strongly associated with silent brain infarction, which will lead to symptomatic stroke and cognitive decline in the future.

TRANSLATIONAL OUTLOOK: The long-term prognosis of patients with aortic atherosclerosis should be investigated to determine the future risk of symptomatic stroke and cognitive decline. There is an urgent need to find appropriate management and treatment to stabilize aortic plaque.
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APPENDIX For supplemental figures, videos, and a table, please see the online version of this paper.