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EDITORIAL COMMENT

Spontaneously Ruptured Aortic Plaque

A Potential Cause for Frequently Observed Cerebral Infarct?*

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Ischemic stroke with embolic features but without identification of exact embolic sources is termed embolic stroke of undetermined source (ESUS).[1] Advanced neuroimaging techniques such as transesophageal echocardiography (TEE) and cardiovascular magnetic resonance (CMR) imaging provide improved detection of cardiac sources of embolism caused by conditions such as patent foramen ovale and left ventricular and left atrial thrombi.[2] Rupture of nonstenotic aortic, carotid, and intracranial atherosclerotic plaque is another potential source of ESUS. Autopsy reports[3] indicated that the prevalence of ulcerated plaques in the aortic arch was as high as 28% in patients with pathologically proven ischemic stroke. Of greater note, 22% of patients with a known cause of ischemic stroke had ulcerated aortic plaque, whereas 61% patients without a known cause of ischemic stroke had ulcerated plaque. Nevertheless, it still seems insufficient to deduce causality based on presence of aortic plaque alone.

Earlier studies of aortic plaques used TEE to investigate the impact of aortic plaque thickness and morphology on the risk of future ischemic strokes. It was reported that the incidence of recurrent brain infarction was significantly higher in patients with an aortic wall thickness >4 mm (11.9 per 100 person-years) compared with those with thickness <4 mm (<3.5 per 100 person-years).[4] The risk of vascular events associated with aortic plaque thickness (≥4 mm) is markedly increased by the absence of plaque calcifications, but not by the presence of plaque ulceration.[5] More recently, 3-dimensional multicontrast black-blood CMR identified vulnerable plaques (according to modified American Heart Association (AHA) classification of atherosclerotic plaques) and estimated the risk of embolization in ESUS patients[6]; of those patients with plaques ≥4 mm, 7 out of 40 stroke patients (17.5%) and 2 out of 60 control subjects (3.3%) ($P < 0.001$) had vulnerable AHA type VI plaques. Among the 7 stroke patients, 6 had potential pathways to cerebral embolization, with plaques located in the aortic arch (n = 3) and proximal descending aorta (n = 3), respectively.

However, these techniques do not show the dynamic embolization of debris directly from the so-called spontaneously ruptured aortic plaques (SRAPs). Nonobstructive general angioscopy (NOGA) directly visualizes the surface of vessel with high spatial resolution and records dynamic images of SRAPs as more direct evidence of aortogenic mechanism in ischemic stroke.[7,8] Among plaques, chandelier plaques that reflect light from the angioscope appeared like cholesterol crystals. Previous studies reported the incidence of SRAP as high as 80.9% in patients with or suspected of having coronary artery disease, but 45.8% of these incidents occurred below the diaphragmatic level.[8] In the EAST-NOGA (Evaluation of Atherosclerotic and Rupture Events by Non-obstructive General Angioscopy) study,[9] the presence of 12 or more aortic plaques was a significant predictor for composite end point events (including cardiovascular death, stroke, and myocardial infarction) during a median follow-up period of 13 months. The contribution of SRAPs to ischemic stroke, however, was still difficult to estimate.

In this issue of *JACC: Asia*, Higuchi et al[10] used NOGA (from origin to proximal descending aorta) to assess the dynamic morphology of aortic plaques in patients with coronary artery disease. Brain magnetic resonance imaging (MRI) was performed within 3 months of NOGA.[10] Proximal aortic SRAPs were

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correlated with the occurrence of ischemic cerebral infarcts with an odds ratio of 14.3. Ischemic stroke was found in 29% of subjects, and subcortical white matter infarctions with relatively small lesions accounted for a large proportion (31 of the 33 cases), which could be consistent with an embolic etiology. Symptomatic brain infarction accounted for 18% (6 out of 33 cases), and the rest were silent. Unlike most studies that used stroke symptoms or death as an end point, this study employed MRI-positive infarct, which would also capture asymptomatic events.

One concern is the possibility of iatrogenic strokes caused by NOGA. It has been argued that the intravascular imaging device could contribute to rupture of aortic atherosclerotic plaques through direct contact.[11] The EAST-NOGA study revealed that there were no reports of acute aortic injury or thromboembolism during the procedure and within 48 hours after NOGA.[9] In the study by Higuchi et al, no new diffusion-weighted MRI-positive lesions were detected in the cohort within 3 months after NOGA.[10] Nevertheless, more data are needed on the safety of NOGA, which should be assessed in future relevant studies.

The study mentioned recent trials finding that oral anticoagulants (rivaroxaban and dabigatran) were not superior to aspirin in preventing recurrent stroke after ESUS.[12,13] However, the use of statins or aspirin in the present study was not mentioned. Statins and other lipid-lowering agents contribute to plaque stabilization. Aortic atherosclerotic plaque may regress with the use of high-dose statins on high-resolution vessel-wall MRI,[14] and it would be intriguing to investigate plaque changes associated with treatment as assessed by NOGA.

This study has several limitations. The first is the lack of baseline MRI information, which makes it difficult to assess the severity of baseline conditions and the age of the detected lesions on postprocedure MRI. The second is that distinguishing white matter hyperintensity and old lacunar infarcts can be challenging in imaging. The third issue is the need to exclude etiologies, such as covert atrial fibrillation, that would likely confound the results. For studies identifying the origin of embolus (eg, identifying aortogenic in this study), it is difficult to exclude all other sources in a population with a high risk of atherosclerosis (eg, in patients with coronary artery disease). However, attempts should be made in a comprehensive examination protocol to assess the conditions of other vascular beds for future studies.

This study should stimulate future studies to investigate unsolved issues. As more advanced imaging techniques arise, comparison between modalities, including TEE, structural CMR, and NOGA, could help to determine differential value and applications. The infarcts in the follow-up scans should be compared with the baseline scans, and the age of the infarcts should be stratified and analyzed. More comprehensive and convincing follow-up indicators should be included to reflect the cerebral damage/dysfunction, such as small vessel disease burden, functional measurements (eg, cognitive functions), and mid- to long-term prognosis.

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