Silent ischemic lesion laterality in asymptomatic internal carotid artery stenosis relates to reduced cerebral vasoreactivity

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Abstract

Background: We investigated the relationship between silent ischemic lesions, defined as hyperintense lesions on T2-weighted magnetic resonance imaging scans of brain white matter and cerebral hemodynamics (baseline cerebral blood flow and cerebral vasoreactivity).

Methods: Between January 2007 and December 2012, 61 patients with asymptomatic internal carotid artery stenosis were evaluated for asymptomatic silent ischemic lesions, acute infarction, and cerebral hemodynamics. Patients were divided into 2 groups based on silent ischemic lesion distribution; the Symmetry group (n = 34) included patients who showed symmetrical distribution of lesions (or had no lesions), and the Asymmetry group (n = 27) included patients with a greater number of lesions in the ipsilateral than that in the contralateral hemisphere. The Asymmetry group was further divided into Internal (n = 15) and External (n = 12) types.

Results: Two External-type patients (17%) showed spotty asymptomatic acute infarction in the ipsilateral hemisphere. There were no significant differences in patient characteristics, histopathological findings, vascular risk factors, or cerebral blood flow values between the groups. The mean cerebral vasoreactivity value in the ipsilateral hemisphere for the Internal type was 13.0 ± 15.2% (range: −11.4% to 41.6%), which was significantly lower than values of the contralateral hemisphere (36.7 ± 20.8%; range: 3.9% to 75.7%; P < .01) and ipsilateral hemispheres of the other groups (P < .01).

Conclusions: The finding that increased ipsilateral asymmetrical silent ischemic lesions correlated with cerebral vasoreactivity reduction may help predict the risk of cerebral infarction in patients with asymptomatic internal carotid artery stenosis.

Key Words: Cerebral blood flow, cerebral vasoreactivity, internal carotid artery stenosis, silent ischemic lesions
INTRODUCTION

The therapeutic strategy for patients with asymptomatic carotid artery stenosis is highly controversial. The results of the Asymptomatic Carotid Atherosclerosis Study showed that patients who underwent carotid endarterectomy (CEA) had a reduced risk of stroke compared with that in patients who were treated medically. Clinical outcomes of medical treatment have improved with the development of medications such as statins, and a recent report revealed a low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment. Conversely, various risk factors of cerebral infarction have been reported in recent years. Kakkos et al. suggested that, in patients with asymptomatic carotid stenosis, silent embolic infarcts on computed tomography were associated with an increased risk of neurologic events and stroke. Altaf et al. suggested that leukoaraiosis was associated with intraplaque hemorrhage in patients with symptomatic carotid artery disease. Various vascular factors, including hypertension, hyperlipidemia, and diabetes mellitus, as needed.

Magnetic resonance imaging procedures

MR imaging was performed using a Magnetom Sonata 1.5T system (Siemens, Erlangen, Germany) with standard neck array and spine array coils. Plaque imaging was performed using magnetization-prepared rapid gradient-echo (MPRAGE) in transaxial sections using a null blood condition (effective inversion time, 660 ms; TR, 1500 ms) and the water excitation technique to suppress fat signals. All patients underwent T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and MPRAGE. Silent ischemic lesions (SILs) were defined as asymptomatic hyperintense lesions in the white matter of the brain on FLAIR images.

Two observers, a neurosurgeon and a radiologist, evaluated the signal intensity of the plaques on MPRAGE relative to the signal intensity in the adjacent muscle (typically the sternocleidomastoid muscle), as measured by placing a circular region of interest, 5–8 mm in diameter, on a standard console of the clinical MR system. If the plaque displayed a signal intensity of 200% or more of the muscle intensity in any area or section in the plaque, it was categorized as “high signal intensity.” Otherwise, the plaque was categorized as “low signal intensity.”

Single-photon emission computed tomography procedures

Preoperative clinical single-photon emission computed tomography (SPECT) studies followed the dual table autoradiographic (DTARG) protocol, with dual administration of iodoamphetamine. Briefly, 2 dynamic scans were acquired in quick succession, with a 2-min interval between them. The first scan covered the initial 0- to 28-min period and the second was acquired between 30 and 58 min. At 4 min per frame, each of the 2 dynamic scan periods produced 7 frames. One-minute long infusions of $^{123}$-iodoamphetamine...
were administered into the antecubital vein at 0 and 30 min. Acetazolamide (17 mg/kg, 1000 mg maximum) was administered intravenously 20 min after the first and 10 min before the second iodoamphetamine injection. Projection data for the acquisition duration of the first and second scans were summed and reconstructed. SPECT data provide quantitative information on CBF at rest and after an acetazolamide challenge, and thereby provide information about the vascular reserve and the severity of hemodynamic brain ischemia. Regional vascular reserve was defined as the ratio of the difference between acetazolamide-activated regional CBF (rCBF) and resting rCBF to resting rCBF: Regional vascular reserve \( = \frac{(\text{acetazolamide-activated rCBF/resting rCBF} - 1) \times 100}{\%}\). The \(^{123}\text{I}-\text{iodoamphetamine autoradiographic method was performed postoperatively for all the patients. This method uses a single iodoamphetamine administration to assess CBF at rest.}^{[14]}\) The image reconstruction process was the same as that used for the DTARG protocol.

**Histopathological procedures**

The CEA specimens were immediately fixed in HistoChoice® Tissue Fixative (Amresco, Inc., Solon, OH, USA) for 48 hours and decalcified with ethylenediaminetetraacetic acid. Subsequently, the specimens were divided into 5-mm blocks (starting at the CA bifurcation and extending rostrally along the ICA) and embedded in paraffin. From each 5-mm block, 3-µm sections were obtained and labeled with hemotoxylin, eosin, and Masson's trichrome stain for histological evaluation. The necrotic core was defined as a core area of atheromatous plaques consisting of necrotic macrophages, cholesterol crystals, and (occasionally) hemorrhage. The proportion of the necrotic core area to the total plaque area (NC proportion) was measured using a computer-based morphometric system (WinRoof, Mitani Co., Ltd., Ishikawa, Japan). Each section was histopathologically evaluated by an experienced histopathologist.\(^{[9],[12]}\)

**Statistical analysis**

Differences in the bilateral hemodynamic parameters were statistically compared using repeated-measures analysis of variance (ANOVA) with post-hoc Tukey tests. Differences in the hemispheric values were compared using ANOVA and post-hoc Scheffe’s F-test. Qualitative patient demographics were compared using the Chi-square test. A probability value of <.05 was considered a statistically significant difference.

**RESULTS**

The 61 study patients were divided into 2 groups based on the distribution of the SILs; the Symmetry group (\(n = 34\)), which included patients who showed symmetrical distribution of SILs or did not have any SILs, and the Asymmetry group (\(n = 27\)), which included patients with a greater number of SILs in the ipsilateral than in the contralateral hemisphere. The SILs of the patients in the Asymmetry group were further divided into 2 subtypes [Figure 1]; the Internal type (\(n = 15\)), in which the patients had only subcortical SILs, and the External type (\(n = 12\)), in which the patients had SILs involving the cortex. The patients who had both components were placed in the External type. Table 1 shows a summary of the clinical data in each group. There were significantly more men in the External type subgroup. There were no differences in the age, stenosis rate, arterial fibrillation, cardiovascular disease, and vascular risk factors between the groups.

The hemodynamic parameters measured with SPECT are presented in Table 2. The mean CVR value in

![Figure 1](image-url.png)

Figure 1: Patients were classified into groups on the basis of the distribution and location of silent ischemic lesions. (A) Silent ischemic lesions (SILs) were defined as asymptomatic hyperintense lesions on fluid-attenuated inversion recovery images in the white matter or as periventricular lesions (arrows). (B) Cases with symmetrical distribution of SILs (B1) or without SILs (B2) were categorized into the Symmetry group. (C) Cases with asymmetric SILs in the subcortical or deep white matter only were classified as the Asymmetry group (Internal type). (D) Cases with asymmetric SILs involving the cortex were classified as the Asymmetry group (External type).

| Table 1: Summary of the clinical data for each study group |
|----------------------------------------------------------|
| **Symmetry** \((n=34)\) | **Asymmetry** | **P** |
| **Age (y)** | 69.9±5.8 | 72.5±3.9 | 70.4±5.0 | 0.298 |
| **Sex (male)** | 29 (85%) | 10 (77%) | 12 (100%) | <.05 |
| **Stenosis (NASCET\%)** | 77.1±10.1 | 83.2±7.4 | 79.2±10.4 | 0.59 |
| **Hypertension** | 18 (53%) | 8 (53%) | 6 (50%) | 0.981 |
| **Hyperlipidemia** | 12 (35%) | 6 (40%) | 4 (33%) | 0.742 |
| **Diabetes mellitus** | 7 (21%) | 7 (47%) | 3 (25%) | 0.183 |
| **Arterial fibrillation** | 1 (3%) | 0 (0%) | 1 (8%) | 0.427 |
| **Smoking** | 8 (24%) | 4 (27%) | 4 (33%) | 0.806 |
| **Cardiovascular disease** | 12 (35%) | 8 (53%) | 3 (25%) | 0.763 |

Data are presented as mean±standard deviation or \(n\) (%). NASCET: North American Symptomatic Carotid Endarterectomy Trial criteria.
the ipsilateral hemisphere for the internal type was 13.0% ± 15.2%, ranging from −11.4% to 41.6%. This was significantly lower than the mean values in the contralateral hemisphere (36.7 ± 20.8%, range: 3.9% to 75.7%, P < .01) as well as in the ipsilateral hemispheres of the other groups (P < .01). There were no significant differences in CBF values between the groups.

Table 3 shows the characteristics of the carotid plaques and asymptomatic acute infarctions in each group. DWI revealed spotty asymptomatic acute infarctions in the ipsilateral hemisphere of 2 patients (17%), both of whom belonged to the External type subgroup. Histopathological examination was conducted to validate the MPRAGE findings. The evaluable histopathological findings of 20 patients, including 10 patients in the Symmetry group, 5 in the Internal type subgroup, and 5 in the External type subgroup were examined in this study; no statistical differences were observed, including in the NC proportion and high signal intensity rate in MPRAGE, among the three groups.

**DISCUSSION**

Previous studies have shown that the extent of white matter lesions correlates with acute subcortical infarcts, which may be a risk factor for subsequent stroke. These studies suggested that several white matter lesions might, at least in part, represent sequelae of multiple acute infarcts of the deep white matter. Our present findings are consistent with these data, as we detected asymptomatic acute infarctions on DWI in the Asymmetry group.

A significant association between the presence of white matter hyperintense lesions and the instability of carotid plaques as detected with MR plaque imaging, including the risk of intraplaque hemorrhage, has been reported in patients with symptomatic carotid artery disease. In the present study, there were no statistically significant differences in the instability of the carotid plaques among the different groups. We speculate that the relatively small number of patients in each subgroup contributed to differences not being significant. That, together with the fact that the border of each group was judged by two observers subjectively, represented limitations in the present study. Similarly, the histopathologic findings did not show significant instability in the External type. Because the CVR value was significantly lower in the Internal type, we postulated that hemodynamic factors are mainly responsible for the etiology of internal asymmetry SILs. On the other hand, we considered the possibility that embolic factors, in addition to hemodynamic factors, may be associated with the instability of the carotid plaques in the External type. However, neither ulceration nor histopathologic findings showed evidence of significant instability in the External type, although the number of patients was small. A previous immunohistochemical study at our institution showed an association between thin fibrous caps possessing adipophilin-positive macrophages and intraplaque hemorrhage, and suggested that the CEA procedure was suitable for patients with unstable carotid artery plaques. Furthermore, it has been reported that atherosclerotic carotid artery plaques with high signal intensity on MPRAGE sequences show a higher incidence of instability, including large necrotic cores with intraplaque hemorrhage, in patients with high-grade stenosis. Because of the retrospective nature of the present study, all patients underwent the CEA procedure, and this may represent a potential selection bias.

In this series, two cases of asymptomatic acute cerebral infarction detected with DWI were found to consist of multiple small lesions in patients with severe carotid artery stenosis. In a recent study that investigated the association between acute stroke patterns on DWI and carotid artery lesions, several disseminated small subcortical infarctions were recognized as a new stroke pattern, which were thought to be caused by multiple
emboli or by the breakup of one large embolus.\textsuperscript{2,25} Conversely, several reports have stated that the recurrence of deep white matter infarction in patients with critical carotid artery disease may be related to hemodynamic compromise due to limited collateral circulation;\textsuperscript{3,26} one recent study concluded that both embolic and hemodynamic mechanisms participate in border zone infarctions.\textsuperscript{4}

The main strength of our study was the comparison of FLAIR images as an advanced MR imaging tool, with quantitative CBF and CVR values measured using the DTARG protocol and \textsuperscript{123}I-Iodoamphetamine.\textsuperscript{5} FLAIR imaging has been reported to be more sensitive than T2 sequences for detecting small ischemic lesions;\textsuperscript{17} however, studies comparing \textsuperscript{123}I-isopropyl-Iodoamphetamine SPECT (which is a quantitative CBF evaluation method) and FLAIR image findings are rare. According to previous reports on the topic, the ACZ challenge, which assesses CVR, is useful in evaluating the residual vasodilatory capacity of resistance vessels and is a predictor of subsequent stroke in symptomatic patients with major cerebral arterial stenosis-occlusive disease. The CVR values in regions of hypoperfusion are determined by the development of collateral circulation from regions with a sufficient blood supply.\textsuperscript{11,24,28} In a long-term prospective study, Kuroda et al. reported that decreased levels of both CVR and CBF represented an increased risk of stroke recurrence.\textsuperscript{19} In addition, Ogasawara et al. reported that reduced CVR values upon ACZ challenge, as obtained by \textsuperscript{133}Xe SPECT, were significantly associated with an increased stroke recurrence rate (34.8\%) in patients with symptomatic cerebrovascular disease.\textsuperscript{22} In the present study, the CVR value in the ipsilateral hemisphere was significantly lower than the corresponding values in the Internal type of the Asymmetry group. The development of SILs may be caused by factors such as hemodynamic impairment or a damaged blood–brain barrier, and may be different between the two groups.

**CONCLUSION**

In conclusion, we report that the presence of increased asymmetrical SILs in the deep white matter is associated with impaired CVR, which may indicate a poor collateral network in the ipsilateral hemisphere. These findings may help predict the risk of cerebral infarction in patients with asymptomatic ICA stenosis.

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**Conflicts of interest**

There are no conflicts of interest.

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