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Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid stenosis

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Abstract

Objective. To investigate the association between carotid plaque characteristics and the occurrence of cerebral microemboli signals (MES) and subsequent ischemic events in patients with asymptomatic carotid stenosis (ACS). Design. Sixty-two asymptomatic patients with 50–99% carotid stenosis underwent transcranial Doppler (TCD) monitoring to determine the relationship between MES and plaque characteristics. The patients were followed for 1 year, and the incidence of transient ischemic attack (TIA)/stroke was studied. Results. MES were found in 10/62 of the patients at baseline, and there was a significant difference between the patients with moderate stenosis and those with severe stenosis on the presence of MES (p = 0.016). Furthermore, MES were more frequently found in patients with irregular and/or heterogeneous plaques than in those with regular (p = 0.028) and/or homogeneous plaques (p = 0.021). The incidence of TIA/stroke occurred more frequently in patients with MES than those without MES (p = 0.009). The proportion of progressive carotid stenosis was 4/50 in the patients with 50–99% stenosis during 1 year follow-up. Conclusion. Asymptomatic patients (with 50–99% carotid stenosis) with MES presented a significantly increased frequency of severe stenosis, with irregular and heterogeneous plaques.

Key words: Carotid stenosis, embolic signal, ultrasonography, transcranial Doppler, transient ischemic attacks, stroke, morphology

Carotid artery stenosis has been recognized as an important cause of ischemic stroke for several decades. Of all the ischemic events associated with carotid stenosis, the most frequent cause is embolism. Increasing evidence suggests that cerebrovascular microembolic signals (MES) detected using transcranial Doppler (TCD) have clinical significance. MES have been found to predict either combined stroke or TIA (1) or stroke risk alone (2) in patients with carotid stenosis.

Carotid endarterectomy (CEA) has been proven to decrease MES rapidly and be beneficial for patients with severe carotid stenosis (3). Though there is a significant reduction in stroke risk by CEA surgery, this reduction is small. The number of patients that would need to be treated to prevent one event per year is very large. Therefore, improved methods of identifying those patients at high risk for cerebral embolic events and suitable for CEA are necessary, particularly among those with severe asymptomatic carotid stenosis (ACS). Previous studies have suggested that the detection of MES could be of great importance for the identification of a high-risk group.

The presence of microemboli in patients with carotid stenosis indicates the existence of unstable plaques which act as active embolic source, and it makes the assessment of plaque characteristics important. The increased presence of MES is associated with the carotid stenotic degree and plaque...
ulceration on angiography (4,5), and some studies have suggested that carotid stenosis and its progression might be independent predictors of vascular events (6,7). However, a contrary opinion is also proposed (8). Furthermore, while investigators have shown that plaque surface irregularities or heterogeneous textures are associated with an increased risk of ipsilateral ischemic stroke (9,10), others still consider this relationship to be uncertain. Therefore, in this study, we performed ultrasonography and TCD monitoring on patients with ACS (≥50%) to study the correlation of MES with carotid plaque characteristics. Simultaneously, the relationship between MES and the risk of ischemic events was investigated in a prospective study.

Materials and methods
Subjects recruitment and demographic characteristics
Seventy-three patients with 50–99% internal carotid stenosis were chosen as the subjects. The patients were referred for asymptomatic stenosis, defined as no symptoms in the ipsilateral carotid artery territory for at least 2 years. All patients underwent clinical history inquisition, neurological examination, electrocardiography, cerebral CT and/or MRI and carotid duplex ultrasound. Patients with potential cardiogenic sources of emboli, poor temporal insonation window, poor life expectancy or intervention surgery within the next several days were excluded.

The eligible and consenting subjects participated in an extensive baseline evaluation that included standard questionnaires, physical examination, and laboratory examination. The standard questionnaires included the history of vascular disease, risk factors and current medication use such as antiplatelet (aspirin), antihypertensive and statins medication. Biochemical parameters were measured in our testing laboratory. This study was approved by the hospital ethics committee, and written informed consent was obtained from all patients.

Carotid duplex ultrasonography
Carotid duplex ultrasonography was performed using GE Vivid 7 (Horten, Norway) and Philips IE33 ultrasound system (USA) with high-frequency linear array transducer. The ultrasonography was performed by an experienced sonographer who was unaware of the clinical profile of the patients. The severity of carotid stenosis was classified into moderate (50–69%) and severe (70–99%) stenosis according to the published criteria (11). Plaque morphology characteristics were studied on the surface and texture. The surface morphology was categorized as regular or irregular, and the plaque texture was designated as homogeneous or heterogeneous (12). All images were recorded onto a disk for integrated evaluation. The degree of stenosis and plaque morphology was assessed independently by two additional investigators who were blinded to the patient’s clinical status.

Transcranial Doppler monitoring
TCD recordings were made from the middle cerebral artery (MCA) ipsilateral to the carotid stenosis via the transtemporal route. These studies were performed with a pulsed Doppler machine (EME-Nicolet Pioneer TC-2021, Germany) with a 2-MHz pulsed-wave Doppler ultrasound probe. The subjects were placed in a supine position and the MCA was identified via the transtemporal window, then the transducer was fixed with an external fixation device. The insonation depth was set with range of 50–56 mm. The axial width of the sample volume was set from 12 to 15 mm, and it was kept constant thereafter for each patient. The TCD recordings were performed for up to 1 hour on two occasions a week apart, and these results were regarded as the baseline assessment. The whole monitoring was done by an experienced investigator who was blinded to the results of the clinical evaluation. All MES were automatically saved onto a computer hard disc, and the audio signals were recorded onto an audiotape for subsequent off-line analysis.

All off-line MES analyses were performed blinded to the patient’s clinical information with specially designed software. The recordings were played back through the same TCD system and a trained observer reviewed the whole study and noted the timing of possible MES. Two additional observers, blinded to the patients’ details, also inspected each possible MES according to the criteria of the Ninth International Cerebral Hemodynamic Symposium (13) and the standards of the International Consensus Group on Microembolus Detection (14), with an intensity threshold of ≥7 dB. Only the signals detected by the three observers were included in the subsequent analysis.

Follow-up
TCD monitoring was performed biannually, and the endpoints for this study were ipsilateral stroke, TIA, carotid intervention surgery or non-stroke death. The occurrence of neurological events or death was determined by neurologists through related inspection and death certificate. Duplex ultrasonography was repeated for evaluating the progression of carotid stenosis at 1 year follow-up. Carotid stenosis
by re-examination was classified into four categories: <50% stenosis, 50–69% stenosis, 70–99% stenosis and occlusion. Disease progression was defined as a change of stenosis classification by at least one category, from a less severe to a more severe one. All the studies were performed by the same researchers and the criteria were in accordance with that of enrollment.

Statistical analyses

All statistical analyses were performed using SPSS software (version 13.0.0; SPSS). Chi-square test was used to compare groups with respect to categorical variables. A Kaplan-Meier survival analysis was performed and the log-rank statistic was computed to compare event-free survival between MES-positive and MES-negative cases. P-value <0.05 were considered statistically significant.

Results

Carotid stenosis assessment and MES detection

Of the 73 ACS patients, 11 were considered but not recruited, and 62 patients remained for subsequent analysis. The mean age of included patients was 65.50 ± 8.38 years (range, 48–81 years). At entry, all 62 subjects underwent duplex carotid ultrasonography, and no obvious differences were observed between the patients investigated by the GE Vivid 7 or the Philips IE33 machines. The analysis was performed on carotid arteries without occlusions on ultrasound imaging. Forty-three patients had 50–69% carotid stenosis and 19 had 70–99% stenosis (Figure 1A–D).

We obtained 123 TCD recordings at baseline, and no patients experienced hemispheric TIA or stroke during the recordings. Microembolic signals (Figure 1G) were detected in eight of the 62 patients on the first TCD scanning. Repetition of the recording 7 days later gave a cumulative yield of ten MES-positive patients. Of the 123 patient-hours recorded, 13 h were MES-positive and the rate of MES was 1.2 ± 0.7 per h.

Relationship between demographic characteristics and MES

The analysis of demographic characteristics in the subjects with and without MES (data not shown) indicated that there were no differences in traditional risk factors (ie, age, sex, smoking status, hypertension, and diabetes). Patients with MES were slightly, but not significantly, likely to be taking aspirin than those without MES, and there were no significant differences in MES status among patients on anti-hypertensive or statin treatments either (p > 0.05). The differences in laboratory tests were not significant, except for the plasma total homocysteine that was markedly higher in patients with microemboli.

Correlation between morphology of plaques and MES

An irregular surface was recorded in 33 of 62 patients, and heterogeneous plaques in 26 of 62 patients. The relationship between plaque characteristics and MES are shown in Table I. The MES were more frequently encountered in patients with severe stenosis than those with moderate stenosis (7/10 vs. 3/10, p = 0.016). Plaque surface studies indicated that patients with irregular plaques were more likely to have MES than those with regular plaques (9/10 vs. 1/10, p = 0.028). In the patients with MES, three were identified with ulceration and two with thin and non-intact fibrous caps (Figure 1E). In the MES-positive group, significantly more heterogeneous than homogeneous plaques were observed (8/10 vs. 2/10, p = 0.021) (Figure 1F).

MES detection during follow-up and subsequent events

The subjects were followed for 1 year after the initial evaluation except for 12 patients. The reasons of absence were: seven were censored because of cerebral ischemic events, death or carotid stenting, three voluntarily left the study, and two did not reach 1 year. At the follow-up visit, seven MES were identified from 108 TCD monitorings; four patients had suffered ipsilateral cerebral ischemic symptoms (1 stroke, 3 TIAs), which were all ipsilateral to the baseline MES; and three patients had suffered myocardial infarctions (MIs), and two died as a result (Table II). Significantly more emboli were found at the follow-up visit in the MES-positive group compared to the MES-negative group. The occurrence of ischemic cerebral events (TIA/stroke) was present in 3/10 of patients with MES vs. 1/52 of those without MES. There was no significant difference in MI or death between the two groups. Figure 2 shows the Kaplan-Meier curves of survival-free of stroke or death among patients with MES compared with those without MES at baseline, which were significantly different from each other (log rank p = 0.006).

Progression of carotid stenosis

At 1 year follow-up, duplex ultrasonography was performed on the remained 50 subjects again. Of the subjects re-examined, progression had occurred in four patients. One patient with severe stenosis at enrollment was found to have an occlusion, and not long after, this patient suffered a stroke. Three
Figure 1. Imaging and microembolic signals in asymptomatic patient with severe carotid stenosis. (A) Ultrasonography showed a severe stenosis in right ICA in the longitudinal section. (B) The velocity within the area of stenosis was very high. (C) Angiography identified the stenosis as severe. (D) MRI showed no ischemic lesions in the ipsilateral carotid territory, except for some lacunar infarctions around the lateral ventricle. (E) Left, an ulceration (white arrow) could be found and there was no obvious fibrous cap on the surface of the plaque; right, the color Doppler flow imaging demonstrated the existence of ulceration (black arrow). (F) The plaque in the area of stenosis was identified as heterogeneous in the transverse section. (G) The high-intensity transit signal (white arrow) on the spectrum detected by transcranial Doppler demonstrated the presence of microemboli.
patients progressed from 50–69% to 70–99% stenosis and one patient regressed from 50–69% to <50% stenosis, and 45 patients remained unchanged. These four subjects with progressive disease were identified roughly as not taking effective medication and/or maintaining bad habits (data not shown).

**Discussion**

Here we found that MES were present in 10/62 of the patients with ACS (≥50%), and 1 year later, the accumulative occurrence of microemboli and the incidence of TIA/stroke in patients with MES were both significantly higher than those without MES, which provides further evidence that MES are associated with an increased risk of TIA/stroke in patients with ACS. This also confirms the reported clinical significance of MES in risk stratification. Moreover, it is worth noting that MES were more frequently found in patients with severe stenosis, irregular and/or heterogeneous plaques than in those with moderate stenosis, regular and/or homogeneous plaques, which indicates that the characteristics of plaques in patients with carotid stenosis play an important role in the presence of MES, and hence may do good to the occurrence of the ischemic events. In addition, the aggravation of carotid stenosis occurred in 4/50 patients and the others remained no obvious progression.

In our study, the incidence of MES is slightly higher than that of other studies (1,15). The main cause may be that the patients did not undergo transesophageal echocardiography, and the emboli from heart or aortic arch may have played a role in cerebrovascular embolism and have caused the proportion of MES rise. The proportions and frequencies of MES in patients with ACS reported in previous studies are very different. A number of factors may account for these dissimilarities, including differences in populations, degrees of carotid stenosis, equipment characteristics, experimental designs, criteria used to identify MES or inter-observer reproducibility.

Study with ambulatory TCD demonstrates that the pattern of embolization is not random but exhibits temporal clustering (16). This suggests that the carotid atheroma is constantly changing and may sometimes be unstable, with embolization being a dynamic process that may show marked temporal variability. Hutchinson et al. (17) suggested that individual patients could not be reliably classified as emboli-positive or -negative, since the emboli status changes over time. These characteristics indicate that MES detection may be inadequate if only short-duration or one-occasion

recordings are performed. One previous study showed that the proportion of MES-positive ACS patients increased from 20 to 25% when recordings were repeated on three separate occasions (18). In our study with conventional TCD, we found a similarly increased yield (from 8/62 to 10/62), confirming the significance of repeated recordings. Besides, prolonged recording can also increase incidence of MES detection. In a study with ambulatory TCD, after repeating an 8-hour recording 1 week later, the yield of MES-positive asymptomatic patients increased from 26.7 to 46.7% (19). This result indicates that prolonged recording and repeating can provide a good estimation of the true embolic load and may elucidate novel insights into the pattern of embolization.

In this research, we observed a tendency for more severe carotid stenosis to be associated with ultrasonically irregular and heterogeneous plaques, consistent with previous studies (20,21). In recent years, the sonographic characteristics of carotid plaques and their relationship with MES and stroke risk have been the subject of much research; however, whether differences in plaque characteristics can truly predict clinical events is still debated. Hutchinson et al. (17) demonstrated that most patients with severe carotid disease would produce cerebral microemboli over time, and the potential embolic activity of carotid stenosis increased with the degree of the stenosis (22). However, Valton et al. (5) found that the degree of carotid stenosis is not significantly associated with MES. Here, we found that the proportion of MES-positive patients with severe stenosis was significantly higher than those with moderate stenosis, and the occurrence of TIA/stroke was present in all cases of severe stenosis, which suggests that higher degrees of stenosis are associated with the highest risk of ischemic events, consistent with several previous studies (6,9).

Besides stenotic degree, plaque morphology appeared important for the presence of MES. Mayor et al. (23) suggested that irregular plaque surface might be related to MES, but their conclusion was not very definite. In this study, we found that the occurrence of MES was more prominent in irregular plaques than in regular ones, especially in the plaques with ulceration or those with non-intact fibrous cap. Besides, we found that MES were more common in heterogeneous plaques than in homogeneous ones. The former are correlated with the presence of intraplaque hemorrhages, ulceration, and loose stroma, which may become the source of microemboli. More important, ultrasonic plaque morphology may be as critical as severe stenosis in predicting high risk of ischemic events. Some studies have shown that irregularity is associated with an increased risk of vascular outcomes (9,10,24), implicating irregularity being an independent predictor of ischemic stroke. Meanwhile, the echogenicity of carotid plaque has also been implicated as a predictor. It is reported that patients with heterogeneous plaques had a higher incidence rate of TIA/stroke than those with homogeneous plaques (20). Here we found that the occurrence of TIA/stroke was strongly associated with irregular surface (especially ulceration) and/or heterogeneous plaques, indicating the ipsilateral neurological event rate is dependent on plaque characteristics. Our findings suggest that evaluation on plaque morphology is beneficial for screening patients at high risk, and special attention should be paid to patients with severe stenosis, irregular or heterogeneous plaques in clinical practice.

Progressive stenosis is related to many risk factors promoting the development of atherosclerosis. When disease worsening occurs, it is important to monitor the successive changes over some time, especially in the patients with severe carotid stenosis. More importantly, taking effective medication (i.e. CEA or stenting) and refraining the bad habits (i.e. smoking) can slow down the progression of the carotid stenosis, then may avoid the happening of the cerebral ischemic events to some extent.

This investigation has several limitations. First, the number of subjects was still limited and the sample size needs to be enlarged for further study. Second, patients did not undergo transesophageal echocardiography to exclude the possibility of cardiac emboli. Third, techniques for automated MES detection and objective analysis of plaque
characteristics are needed to exclude the affect of subjective decisions.

Conclusions

Our data demonstrate that patients with MES presented a significantly increased frequency of irregular and heterogeneous plaques, and the severe stenosis play a more important role in the presence of MES than moderate stenosis. As MES being marker of the instability of plaques and increased stroke risk, the clinical significance of MES and plaque characteristics needs to be investigated further.

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