Clinical Application of Asymptomatic Embolic Signal Detection in Acute Stroke
A Prospective Study

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Background and Purpose—The detection of asymptomatic embolization with the use of Doppler ultrasound has a number of potential applications in patients with acute stroke. It may provide information on the stroke pathogenesis in individual cases, identify patients with continued embolization, and allow localization of the active embolic source.

Methods—We recruited 119 patients with acute anterior circulation infarction within 72 hours of stroke onset. Transcranial Doppler recordings were possible in 100 (84.0%). Bilateral 1-hour middle cerebral artery (MCA) recordings were made and saved on digital audiotape for blinded offline analysis. When embolic signals were detected during screening of the first recording, simultaneous recording was performed from the ipsilateral MCA and common carotid artery for an additional 30 minutes. In all patients with embolic signals at screening and in matched negative controls, recordings were repeated on days 4, 7, and 14.

Results—Embolic signals were detected in the symptomatic MCA in 16 patients (16%). They were more common in patients with carotid stenosis ($P<0.0001$), occurring in 50% of this group. They were rare in patients with cardioembolic stroke ($P=0.0005$), but they were still present in a third at 2 weeks. In 10 patients, localization of the embolic source was possible by simultaneous recording from the MCA and the ipsilateral common carotid artery.

Conclusions—Continued asymptomatic embolization is common after stroke in patients with carotid artery disease and is still present in a significant proportion at 2 weeks. The technique may identify patients at risk of further stroke for more aggressive antiplatelet therapy; this needs to be tested in large prospective studies. The technique may also allow localization of the active embolic source. (Stroke. 1999;30:1814-1818.)

Key Words: cerebral embolism ■ stroke ■ ultrasonography

Cerebral embolism is the underlying pathogenic mechanism in many cases of stroke. Emboli may arise from the heart; aortic, carotid, and vertebral artery plaques; intracranial atherosclerotic stenoses; or systemic venous thrombosis in the presence of a venous-to-arterial shunt.1 Recently, it has been demonstrated that circulating cerebral emboli can be detected with the use of transcranial Doppler ultrasonography (TCD).1 The technique has been shown to be sensitive and specific in animal2 and in vitro3 models. Asymptomatic embolic signals (ES) have been detected in patients with a variety of potential embolic sources, including atrial fibrillation, carotid artery stenosis, and valvular heart disease.4 The technique has a number of potential applications in patients with acute stroke. In individual patients it may allow identification of the pathophysiological cause and aid in localizing the embolic source. It may also allow identification of patients at high risk of further stroke. It may allow the effectiveness of new antiplatelet therapies to be tested before large clinical trials.

Previous studies have detected ES in patients with acute stroke, but there have been few prospective studies, and even fewer in which localization of the embolic source or determination of the natural history of asymptomatic embolization has been performed. In this study we prospectively recruited consecutive patients with anterior circulation ischemic stroke. We determined the prevalence of asymptomatic embolization in different stroke subtypes. We assessed the practicability of localization of the embolic source by simultaneously performing recordings at multiple points along the arterial tree. In patients who were ES positive on initial recording and in a matched sample of ES-negative patients, we determined the natural history of asymptomatic embolization over the first 2 weeks after stroke onset.
Subjects and Methods

Subjects
One hundred nineteen consecutive patients presenting to an acute stroke unit with acute anterior circulation ischemic stroke within 72 hours of symptom onset were recruited. An acoustic window allowing TCD recordings to be made was present in 100 (84.0%). The study population had a mean age of 69.6 years (SD, ±12.1; range, 42 to 93 years) and consisted of 52 men and 48 women. Subjects were defined as smokers if they currently smoked cigarettes, as hypertensive if they were receiving antihypertensive therapy or if blood pressure was >160 mm Hg systolic or >95 mm Hg diastolic 1 week after stroke onset, and as diabetic if they had insulin-dependent or non–insulin-dependent diabetes mellitus. Hypercholesterolemia was defined as a fasting cholesterol level of >6.0 mmol/L or as treatment with cholesterol-lowering medication. In all patients, antplatelet agents or anticoagulants were not administered until after the first TCD recording. All subjects gave informed consent, and the study was approved by the local hospital research ethics committee.

All patients were evaluated with clinical history, neurological examination, cerebral CT and/or MRI, electrocardiography, and carotid duplex ultrasound. Transthoracic echocardiography was performed in 57 cases, and 5 cases had transesophageal echocardiography. The degree of carotid stenosis was estimated from a combination of the ratio of internal to common carotid artery peak systolic velocity and the B-mode and color flow image.6 With this information, strokes were classified into the following etiologic categories: (1) carotid artery: >50% stenosis in the symptomatic internal carotid artery territory; (2) cardioembolic: a potential cardiac source on transesophageal echocardiography; (3) lacunar: a typical clinical lacunar syndrome7 with an appropriate lacunar infarct or a normal CT or MRI brain scan; (4) coexistent causes: >1 of the above potential causes; and (5) unknown.

All patients were followed up prospectively for the first month to identify recurrent events. In all such cases, repeated neuroimaging was performed.

TCD Recordings
TCD was performed with the use of a Pioneer TC4040 (Nicolet-EME Ltd) with a multidepth 2-MHz transducer. A sample volume of 5 mm and a sweep speed of 5 seconds were used for all patients. A 128-point fast Fourier transform was used for spectral analysis. Fast Fourier transform time-window overlap was 128-point fast Fourier transform was used for spectral analysis. Fast Fourier transform time-window overlap was >60%. The subject was instructed to sit quietly or supine, position, fixed in place with the use of a specially made support with the head immobile to identify patients in whom ES were occurring. All 15 patients identified as ES positive at the time of the first recording were enrolled in a follow-up protocol. In all 30 patients entering this follow-up study, antplatelet agents or anticoagulants were not administered until after the day 7 TCD examination.

In all 15 patients identified as ES positive at the time of the first recording, localization of the embolic source was attempted. An additional 30-minute recording was performed simultaneously from the symptomatic MCA and the ipsilateral common carotid artery (CCA). The same 2 MHz was used for the CCA recordings; this was held in place with the use of a specially constructed support with the transducer mounted in an ultrasound gel block (Urethane Rubber, ATS Laboratories) to offset the probe from the skin and allow insonation at an optimal depth. Mean±SD depth of insonation for the 2 gates for CCA recordings was 35.2±2.8 and 37.2±1.9 mm.

Beam plots for the 2-MHz probe demonstrated that the beam adequately covered the CCA.

For all recordings, the audio Doppler signal was stored on digital audiotape with the use of a TASCAM DA-88 recorder (Teac Ltd). Analysis of recordings was performed offline by an observer (observer 1) who was blinded to the clinical details, time of recording, and subject group. An ES was identified as a predominantly unidirectional short-duration intensity increase, accompanied by a characteristic clicking or chirping sound.8 The results presented in the report are based on this offline analysis rather than the online analysis described above. The online analysis was performed merely to identify ES-positive patients for the follow-up and localization arms of the study. A threshold of >7 decibels was used because this has been shown to increase interobserver agreement without excessive loss of sensitivity.9 Intensity was determined from the color-coded intensity scale on the spectral display. The peak intensity of the ES and the intensity of the background spectra at the same frequency and part of the cardiac cycle, from the preceding or subsequent cardiac cycle, were determined. All possible ES detected were saved and then reviewed by a second experienced observer (observer 2); if both observers agreed that the signal was an ES, it was then included in subsequent analysis. Interobserver reproducibility in identifying ES was assessed by the 2 observers independently analyzing a separate recording that was 105 minutes long and had been prepared from MCA recordings from 6 patients with carotid stenosis. Agreement was calculated with the use of the proportion of specific agreement, which estimates the probability that 1 observer will identify a specific ES if another observer has identified it, with a probability of 1 indicating complete agreement.10 Observer 1 detected 90 ES, and the agreement of observer 1 with observer 2 was 0.92. Observer 2 detected 89 ES, and the agreement of observer 1 was 0.90.

Data Analysis
The rate of embolization was expressed as the number of ES per hour of recording from each MCA, ie, a patient with a successful bilateral recording for 1 hour had 2 hours of successful recording. The difference in the proportion of patients with ES compared with ES-negative patients was determined by χ² tests. The association between the presence of ES and clinical characteristics was determined by χ² tests (with Yates correction when appropriate) or t tests as indicated. Continuous variables were compared with the Mann-Whitney U test. All statistical analysis was performed with SPSS statistical software.

Results

Analysis of First Recording
ES were detected in the symptomatic MCA in 16 patients (16%) within 72 hours after the onset of stroke. This included the 15 patients in whom they were identified at the time of recording and 1 additional patient in whom ES were only detected at the offline analysis stage. The mean number of hours between symptoms and first recording was 32.2 hours (range, 5.5 to 60 hours). There was no difference in time since symptom onset in patients with or without ES: mean (SD) time from onset, 32.9 (10.8) hours versus 32.1 (14.6) hours (P=0.80). The median number (range) of ES in ES-positive patients was 5 (1 to 34) per hour. There was no association between the presence of ES and sex, smoking status, hypertension, diabetes, hypercholesterolemia, previous stroke, or transient ischemic attack. There was no difference between the frequency of prior aspirin use in patients with ES detected on the first recording (9/16, 56.3%) compared with patients in whom ES were not detected (32/84, 38.1%; P=0.18). Atrial fibrillation was present in 1 patient with ES.
Methods. The proportion of patients remaining ES positive is shown in Table 2. In the ES-positive group, 1 patient died during the follow-up period. In 6 of the 100 patients, ES were not detected during the follow-up recordings in any of the ES-negative controls.

Localization of Embolic Source
Localization of the embolic source was attempted in 2 ways. First, we determined whether ES were detected in 1 or both MCAs. In all 16 ES-positive patients, ES were detected in the symptomatic MCA. In addition, in 3 patients ES were detected in the contralateral MCA, suggesting a cardiac or aortic arch source. One of these patients had 2 potential embolic sources, both atrial fibrillation and carotid stenosis on the symptomatic side. In this patient further localization demonstrated signals appearing consecutively in ipsilateral CCA and MCA, suggesting that the source of emboli was proximal to the CCA. Bilateral ES were detected in an additional 2 patients, both with unknown stroke subtype.

Second, in the 15 patients in whom ES were identified at the time of initial recording, an additional 30-minute recording was attempted as we insonated the symptomatic MCA and the ipsilateral MCA simultaneously. In 14 of these patients ES were not detected in patients during the last 15 minutes of the recording.

Recurrence
All patients were followed up prospectively for the first month to identify recurrent events. Six of the 100 patients died within 4 weeks after stroke; 5 had no clear evidence of recurrence in a different territory, while 1 had a recurrent event (9.0%) compared with 24 patients (28.6%) without ES (P=0.06).

When we analyzed the first recording from the symptomatic side, the proportion of patients in whom ES were detected increased from 10 (10%) after 15 minutes, to 12 (12%) after 30 minutes, to 16 (16%) after 45 minutes. There was no further increase in the number of ES-positive patients during the last 15 minutes of the recording.

Correlation With Stroke Subtype
The correlation between ES and stroke subtype is shown in Table 1. ES were significantly more common in patients with carotid stenosis or occlusion compared with the other stroke subtype groups (P<0.0001), occurring in 50% of carotid patients. Eight patients had symptomatic carotid occlusion; 2 of these had coexistent potential cardiac embolic sources. Of the 6 with no other potential source, in 3 (50.0%) ES were detected in the ipsilateral MCA. All of these had contralateral carotid stenosis of >50%. ES were not detected in patients with lacunar stroke. Twenty-two patients were classified as cardioembolic stroke since they had only a potential cardioembolic source (atrial fibrillation in 19, poor left ventricular function and/or akinetic left ventricular wall segment in 3). In this group ES were infrequent, occurring in only 4.5%.

Natural History of Asymptomatic Embolization
Fifteen ES-positive patients and 15 ES-negative controls were enrolled in the natural history study, as described in Methods. The proportion of patients remaining ES positive is shown in Table 2. In the ES-positive group, 1 patient died between each recording, and therefore recordings were performed in 14, 13, and 12 subjects at the 3 follow-up time points. Although the proportion of ES-positive patients fell over time (P=0.0025), half of patients were still ES positive at 1 week, and ES were still present in a third at 2 weeks. ES were not detected during the follow-up recordings in any of the ES-negative controls.

Follow-Up
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Second, in the 15 patients in whom ES were identified at the time of initial recording, an additional 30-minute recording was attempted as we insonated the symptomatic MCA and the ipsilateral MCA simultaneously. Three of 15 ES-positive patients could not tolerate this additional recording because of restlessness, which made it impossible to keep the CCA transducer stationary. During this 30-minute period, additional ES were detected in 10 of the 12 patients. In 8 patients, ES were detected in the MCA only, suggesting a carotid source of emboli; all patients had ipsilateral carotid stenosis on duplex ultrasound. In 2 patients ES were detected in both the MCA and CCA; 1 patient had atrial fibrillation and no carotid disease, while the other, who had atrial fibrillation and carotid stenosis, also had bilateral MCA signals, as described in the preceding paragraph.

Follow-Up
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stroke in a different vascular territory. The only patient who suffered an additional stroke suffered a recurrent stroke in the contralateral carotid territory; this patient had bilateral ES on the initial recording. Death and/or recurrent stroke occurred in a significantly higher proportion of patients in whom ES were detected on the first recording: 4 of 16 (25%) compared with 12 of 84 (14.3%) \( (P=0.026) \). In addition, 2 patients suffered an additional transient ischemic attack, both in the same territory as the presenting event; both were of the lacunar subtype and were ES negative.

**Discussion**

In this prospective study of consecutive patients presenting with acute anterior circulation stroke, we found asymptomatic ES in 16% of patients during a single hour of recording. However, there were marked differences in the prevalence of ES in the different stroke subtypes. They were detected in 50% of patients with carotid stenosis but less frequently in patients with a potential cardioembolic source. We found no ES in patients with lacunar stroke, suggesting that embolization is not important in its pathogenesis. We found no MCA or distal internal carotid artery stenoses in the 100 patients, as identified by TCD velocities and previous validated criteria.\(^{11}\)

In a significant proportion of patients, localization of the embolic source was possible by recording from both MCAs and also by simultaneously recording from the symptomatic MCA and CCA. In 3 subjects the ES were bilateral, suggesting a cardiac or aortic arch source. In 2 of these no cause of stroke had been found, but neither underwent transesophageal echocardiography. This information could be used to identify individuals for further detailed echocardiographic evaluation. The third patient with bilateral ES had 2 potential sources of embolism, a carotid stenosis and atrial fibrillation. The bilateral ES suggest that the latter was the relevant source. This information may be clinically important; the patient might be treated better with anticoagulation for atrial fibrillation rather than urgent carotid endarterectomy. In the same patient, the importance of the atrial fibrillation rather than the carotid stenosis is supported by the detection of ES passing through the CCA and then the ipsilateral MCA when simultaneous recordings were made. In an additional 9 patients, simultaneous recording from the MCA and CCA allowed localization of the embolic source.

Previous studies have reported a prevalence of ES in acute stroke varying from 9.3% to 17.1%. These studies have usually used recording times of 20 to 30 minutes. Earlier studies used online analysis detection of ES, which may be subject to observer bias.\(^{12}\) or the use of currently commercially available automated ES detection software,\(^{13}\) which has been shown to lack specificity.\(^{14}\) In studies in which blinded offline analysis of ES by an experienced observer has been used, ES prevalences of 9%, 19%, 24%, and 40% have been reported.\(^{15–17}\) These are consistent with our results. The lowest figure of 9% was found with a time window of 4 weeks from acute stroke,\(^{16}\) and our results demonstrate that ES frequency declines in the first 2 weeks. Our results also demonstrate the effect of prolonging the recording time on the prevalence of ES; this value would have increased from 12% to 16% by recording for 45 rather than 30 minutes. The high frequency of ES in patients with carotid stenosis has been recently reported in acute stroke,\(^{15}\) and the ES frequency correlates well with that in other studies of patients with recently symptomatic carotid stenosis.\(^{18,19}\) Consistent with the recent results of Koennecke et al,\(^{15}\) we found a low frequency of ES in patients with cardioembolic stroke. This suggests that the pattern of embolization may be different in these patients, perhaps with fewer larger emboli.

There is little information about the natural history of asymptomatic embolization in acute stroke. Sliwka et al\(^{17}\) recorded for 30 minutes at admission and then again 24 and 48 hours later and reported a slight increase in the prevalence of ES on the second recordings, but these time points were narrowly spaced. In patients with carotid artery stenosis, it has been demonstrated that ES are most frequent soon after symptoms.\(^{20}\) Our results demonstrate that the rate of embolization does decline over the first 2 weeks, but in many patients persistent embolization is still occurring at the end of the second week. These patients may be suitable for more aggressive antithromboembolic therapy.

There is increasing evidence that asymptomatic ES in patients with acute cerebral ischemic do identify a subgroup of patients at high risk of further events. A retrospective series of 229 patients examined in a neurovascular laboratory found that ES predicted recurrent ischemic events,\(^{21}\) while a smaller study of acute stroke reported similar findings.\(^{22}\) In our study only 1 patient had recurrent stroke, in a different vascular territory. This patient had bilateral ES on the initial recording. Five patients died, and of these, 3 had ES at presentation. Overall, patients who were ES positive on the first recording had a significantly higher risk of early death or recurrent stroke, but the number of end points was small. It is possible that continuing embolization is merely associated with a worse stroke, but it is also possible that continued ES results in extension of infarction within the initial peri-infarct region. In patients with severe stroke, particularly in a patient in which the embolic source is in 1 carotid artery and therefore recurrence in a different vascular territory is unlikely, this might result in a worsening of neurological status without clear new neurological signs and an increase in mortality. However, the number of strokes and death in our study was very small, making firm conclusions difficult to draw. The risk of early recurrent ischemic stroke is approximately 2% to 4%, and therefore larger studies are required to unequivocally determine whether ES predict stroke risk in this group of patients.

In summary, our results demonstrate that the prevalence of asymptomatic embolization in patients with acute stroke varies markedly among different stroke subtypes, that the technique may provide useful clinical information by identifying and localizing the relevant embolic source, and that continued embolization may be associated with a worse prognosis. Further studies are required to confirm the predictive value of asymptomatic ES and to determine whether they identify a group of patients who may particularly benefit from more aggressive antithromboembolic therapy.

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References


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