Ambulatory Transcranial Doppler Cerebral Embolic Signal Detection in Symptomatic and Asymptomatic Carotid Stenosis

Andrew D. Mackinnon, Rune Aaslid and Hugh S. Markus

Stroke 2005;36;1726-1730; originally published online Jul 21, 2005;
DOI: 10.1161/01.STR.0000173402.88560.ae
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Ambulatory Transcranial Doppler Cerebral Embolic Signal Detection in Symptomatic and Asymptomatic Carotid Stenosis

Andrew D. Mackinnon, MRCP; Rune Aaslid, PhD; Hugh S. Markus, FRCP

Background and Purpose—Transcranial Doppler (TCD) ultrasound can detect asymptomatic emboli in carotid stenosis. Current systems are nonportable and can only record for short durations. A novel ambulatory TCD system allows prolonged recording. We applied this to patients with symptomatic and asymptomatic carotid stenosis to determine patterns of embolization in the 2 conditions and optimal recording protocols.

Methods—Ambulatory TCD recordings were performed in 12 symptomatic and 15 asymptomatic carotid stenosis (≥50%) patients for 8 hours and then repeated on a second occasion.

Results—Nine (75%) of symptomatic subjects had embolic signals during the first recording. In this group, repeating the recording did not increase the proportion of positive patients. In asymptomatic patients, 4 (26.7%) had embolic signals on 1 recording, and this proportion increased to 46.7% after 2 recordings. There was significant clustering of embolic signals demonstrating that the process was nonrandom.

Conclusions—Ambulatory TCD is possible in patients with carotid artery stenosis. By increasing the duration of recording, additional information is provided, particularly in asymptomatic patients. Our results also demonstrate clustering of embolic signals. Our study provides baseline data to allow studies in both asymptomatic and symptomatic carotid stenosis to be planned. **(*Stroke*. 2005;36:1726-1730.)**

Key Words: carotid stenosis ■ stroke ■ ultrasonography, Doppler, transcranial

Transcranial Doppler ultrasound (TCD) can detect asymptomatic circulating cerebral emboli. Such embolic signals (ES) have been detected in patients with a wide variety of embolic sources. Most work has been performed in carotid artery stenosis. In this patient group, ES are more common in patients with known markers of increased risk, including symptomatic status,[1,2] more recent symptoms,[3,4] and plaque ulceration.[5,6] In symptomatic carotid stenosis, the presence of ES predicts future transient ischemic attack (TIA) and stroke risk.[7–9] Whether they have a similar predictive role in asymptomatic stenosis is under investigation.[10] The technique may allow risk stratification and selection for interventions. It may also provide a useful surrogate marker to assess antithrombotic medication efficacy.[11,12]

Conventional TCD uses personal computer (PC)-based systems, which are nonportable or barely portable. For this reason, recordings are usually performed for 30 to 60 minutes. This is a short period for a dynamic process such as embolization. Recently, when the first ambulatory TCD was developed, recordings of up to 5 hours were possible.[13] Further technical developments have allowed the recording period to be extended to 8 hours.

Ambulatory recording may allow better estimation of true embolic load to be obtained and may also provide novel insights into the pattern of embolization. It may allow improved prediction of stroke risk and better estimation of embolic load in therapeutic studies. Before the use of ambulatory TCD in either of these settings, it is important to establish the natural variability in embolization rates and to determine optimal recording protocols. Optimizing recording protocols will also be important for future studies using ambulatory TCD, especially in asymptomatic patients, in whom ES are less frequent and may need a longer overall period of recording.

In this study, we applied ambulatory TCD to patients with both symptomatic and asymptomatic carotid stenosis and repeated it on a second occasion. We used this to analyze temporal variability in embolization and construct optimal recording protocols. We also studied the pattern of embolization in the patient groups.

Subjects and Methods

Subjects

Consecutive patients presenting to a specialized cerebrovascular service with symptomatic or asymptomatic carotid stenosis≥50%, determined

Received April 19, 2005; accepted May 24, 2005.

From the Department of Clinical Neurosciences (A.D.M., H.S.M.), St Georges Hospital Medical School, London, United Kingdom; and Hemodynamics AG (R.A.), Berne, Switzerland.

Correspondence to Prof Hugh Markus, Dept of Clinical Neurosciences, St Georges Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE, United Kingdom. E-mail hmarkus@sghms.ac.uk

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000173402.88560.ae**

TABLE 1. Characteristics of the Two Study Groups

Factor	Symptomatic (n=12)	Asymptomatic (n=15)
Age, years	63.7 (9.8)	70.9 (8.4)
Male Gender, no. (%)	7 (58.3)	11 (73.3)
Hypertension, no. (%)	8 (66.7)	12 (80)
Diabetes mellitus, no. (%)	5 (41.7)	2 (13.3)
Hyperlipidemia, no. (%)	10 (83.3)	13 (86.7)
Ischemic heart disease, no. (%)	3 (25)	3 (20)
Smoker (current or previous), no. (%)	12 (100)	12 (80)
Antiplatelet therapy, no.		
Aspirin	2	13
Aspirin and dipyridamole	4	1
Aspirin and clopidogrel	6	1
Carotid stenosis, % (mean±SD)	78.7 (16.6)	88.8 (8.0)

by standard duplex criteria,[14] were screened for recruitment. Symptomatic was defined as having amaurosis fugax, TIA, or stroke in the territory of the stenosed carotid artery within the last 3 months. Asymptomatic was defined as no symptoms in the ipsilateral carotid artery territory for at least 2 years. Patients with potential cardiogenic sources of emboli, absent window by conventional TCD, or the need for carotid intervention within the next 2 days were excluded. Twenty-three symptomatic patients (9 inpatients and 14 outpatients) were asked to participate. Thirteen (57%) accepted. Of the 10 who declined, 2 were inpatients: 1 refused because of preexisting temporal region tenderness and the other because of length of recordings. Eight of the 10 were outpatients: 7 refused because of inconvenience of the duration of recordings and/or traveling distance to hospital and 1 because of employment commitments. The baseline characteristics of those who declined were as follows: mean (SD) age, 67.9 (13.0) years; 6 male and 4 female; mean (SD) carotid stenosis, 79.4 (17.6)%; and mean time since qualifying event, 33.5 (28.9) days. These were very similar to those who participated (Tables 1 and 2). Eighteen asymptomatic patients were asked to participate, and 15 (83.3%) agreed. Three declined: 1 because of a recent knee operation and 2 because of inconvenience and length of the recordings. Therefore, 28 patients, 13 symptomatic and 15 asymptomatic, were recruited. Mean (SD) stenosis was 78.7 (16.6)% and 88.8 (8.0)% for the symptomatic and asymptomatic groups, respectively. The demographic characteristics and antiplatelet therapy of the patients are summarized in Table 1. Table 2 shows the clinical characteristics of the symptomatic carotid patients including their qualifying event.

Study Design

Ambulatory TCD recordings were performed for 8 hours on 2 occasions in each group of patients; recordings occurred on consecutive days for symptomatic stenosis and were separated by a week for asymptomatic patients. It was not possible to record from 1 of the symptomatic patients because of a technical problem with the probe. Two of the symptomatic patients had only the first recording: 1 patient had carotid endarterectomy before the second recording, and, in 1, the second recording was deleted in error. All asymptomatic patients had both recordings. Three patients (1 symptomatic and 2 asymptomatic) had 7-hour, rather than 8-hour, recordings. These were all outpatients who had transportation commitments. Patients were asked to record any symptoms they had during the recordings on a timesheet. For all patients, antiplatelet medication was left unaltered during the study. All patients gave written informed consent, and the project was approved by the local research ethics committee.

Ambulatory TCD Methodology

The ambulatory TCD equipment design has been described previously.[13] In brief, the battery-powered Doppler measures 18 cm×11.5 cm×2.4 cm and weighs 425 g. The unit has a solid-state flash disk for storage of the quadrature raw Doppler signal. Improved capacity of the flash disk now allows storage of ≈8 hours of data, compared with 5 hours for the original validation study.[13] The batteries are housed in a separate shell. The Doppler unit is connected via a thin flexible tube containing coaxial cable to a 13-mm diameter servo-controlled 2 MHz transducer probe weighing only 40 g, which has a dynamic range of 60 dB. The probe is held in place by mounting on a spectacle frame, as this was found to offer the best combination of optimal fixation and comfort in a pilot study.[13] The inclusion of an event monitor for the patients to record the exact time of any symptoms also allows correlation between symptoms and both hemodynamic disturbance and embolism.

The middle cerebral artery (MCA) Doppler signal was obtained via the transtemporal window with a conventional Doppler unit (Pioneer 4040 with 2 MHz transducer; Nicolet/EME Ltd). Setup and control of the ambulatory module was then performed via a laptop computer connected by a serial port. During setup, the Doppler spectrum was viewed in real time on the laptop, and all functions and settings of the

TABLE 2. Specific Characteristics of Symptomatic Carotid Stenosis Group

Patient No.	Patient Status	Degree of Stenosis (%)	Qualifying Event	Time Since Qualifying Event (days)	Antiplatelet Agent (in addition to aspirin)	ES/h
1	Outpatient	80	TIA	59	Dipyridamole	3.29
2	Outpatient	95	Amaurosis fugax	15	Dipyridamole	2.89
3	Inpatient	60	Stroke	6	Dipyridamole	0.44
4	Inpatient	70	Stroke	8	None	1.06
5	Outpatient	70	Stroke	26	Clopidogrel	0.13
6	Inpatient	99	TIA	56	Clopidogrel	0.19
7	Outpatient	60	Stroke	53	Clopidogrel	0
8	Outpatient	80	Amaurosis fugax	54	Dipyridamole	3.13
9	Inpatient	90	TIA	16	Clopidogrel	0
10	Inpatient	95	TIA	68	Clopidogrel	0.13
11	Outpatient	95	Stroke & A. fugax	8	None	0.06
12	Outpatient	50	Stroke	19	Clopidogrel	0

Aspirin dose, all 75 mg daily, except patient 11 (300 mg).

Doppler unit were remotely controlled and stored. The following settings were used: axial sample volume, 5.2 mm; mean (range) depth of insonation, 50.4 (40 to 56) mm; and pulse repetition frequency, 4629 Hz. When the MCA signal was found, its strength was optimized using the autosearch software module. The unit was then disconnected from the laptop and placed in the pocket of a jacket worn by the patient. Recording continued with unchanged Doppler settings until the unit was powered off or the flash disk was filled to capacity. During the recording, the software monitored the Doppler signal quality, and an autosearch module attempted to restore the vessel insonation during recording if the signal dropped below a preset level. Moreover, at intervals of ≈5 minutes, the search mode was automatically activated to optimize insonation. After the recording the data were transferred from the flash disk to the PC-based computer.

Doppler Signal Analysis

The raw quadrature Doppler audio signal was played from the PC through the signal processor of a conventional TCD machine (Nicolet/EME Pioneer 4040) with the use of a 128-point fast Fourier transform (pulse-repetition rate, 4629 Hz; sweep speed, 5.1 seconds) to give a fast Fourier transform overlap of >50%. All ES analyses were performed blind to individual patient details and the hour of recording. ES were identified as short-duration, high-intensity unidirectional signals in the Doppler spectrum accompanied by a characteristic chirping or clicking sound, using International Consensus Criteria.[15] In addition, an intensity threshold of ≥7 dB was used because this has been shown to increase interobserver agreement.[16] The intensity was calculated from the color-coded intensity scale on the screen, as previously described.[16] Interobserver reproducibility studies were performed on a 2-hour recording comprising six 20-minute recordings from the ipsilateral middle cerebral artery in 6 patients with symptomatic carotid stenosis. Agreement was calculated with the use of the proportion of specific agreement.[16] A probability of 1 indicated complete agreement. Observers 1 and 2 agreed on 80 ES. Observer 1 detected 82 ES, and the agreement of observer 1 with observer 2 was 0.98. Observer 2 detected 88 ES, and the agreement of observer 2 with observer 1 was 0.91.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 11.0.0; SPSS). For each recording, the number of ES per hour was recorded, with a positive hour being defined as 1 containing ≥1 ES. We evaluated the effects of repeating or prolonging recordings in 2 ways. First, we determined the cumulative yield resulting from extending and repeating the recordings. Second, we determined the agreement between recordings using κ statistics. The agreement was considered excellent if $\kappa>0.75$, fair if $\kappa=0.4$ to 0.75, and poor if $\kappa<0.4$. The 3 patients who had 7-hour recordings did so on both occasions, and their results were included in the κ analysis. Because 2 symptomatic patients had only one 8-hour recording performed, they were excluded from analysis for comparisons made between recordings 1 and 2.

To examine the temporal pattern of embolization and to determine whether clustering of ES occurred, 1 further statistical analysis was performed. For those patients with ≥3 ES during the 8-hour recording, the time intervals from the start of the recording until the first ES (t_1) and between the first and second ES (t_2) were determined. We then compared the mean of t_1 with t_2 using the paired-sample t test.

Results

Demographics of the 2 study groups are shown in Table 1. Four hundred eighteen patient-hours of recording were performed in the 12 symptomatic and 15 asymptomatic patients. One of the symptomatic patients, who had presented with recurrent amaurosis fugax, had a further episode of amaurosis fugax during the second recording. The temporal relationship of this event to the embolic signals is shown in the Figure (A). No patients experienced hemispheric TIA or stroke during the recordings. During the study, no patient experienced temporary or permanent skin damage or side effects that resulted in the monitoring procedure having to be curtailed. Scatter plots demonstrating at which time points ES occurred in the individual patients are shown in the Figure, separately for the symptomatic and asymptomatic groups. ES were detected in 9 (75%) of symptomatic subjects and 4 (26.7%) asymptomatic subjects on the first recording and in 9 (75%) and 7 (46.7%) in each group, respectively, after both recordings. The proportion of hours that were ES positive was 55 of 182 (30.2%) and 16 of 236 (6.8%) in the symptomatic and asymptomatic groups, respectively ($\chi^2=40.51$; $P<0.001$). The embolization rates for individual symptomatic patients are shown in Table 2. The mean (SD) ES rate per hour was 0.94 (1.34) in symptomatic and 0.10 (0.13) in asymptomatic patients.

Statistical Analyses for Evidence of Temporal Clustering of Embolic Signals

In patients with high embolic load (patients 1, 2, and 8), there appeared to be temporal clustering of ES with ≥5 ES occurring in a 15-minute period and sometimes within 5 minutes. Five of the 12 symptomatic patients and 1 asymptomatic patient had ≥3 ES during a single 8-hour recording. For these patients, the time interval between the first and second ES (t_2) was significantly shorter than the time interval from the start of the recording and the first ES (t_1); t_2 mean (SD), 36.1 (52.1) minutes; t_1 mean (SD), 98.3 (56.7) minutes; $P=0.016$, confirming clustering.

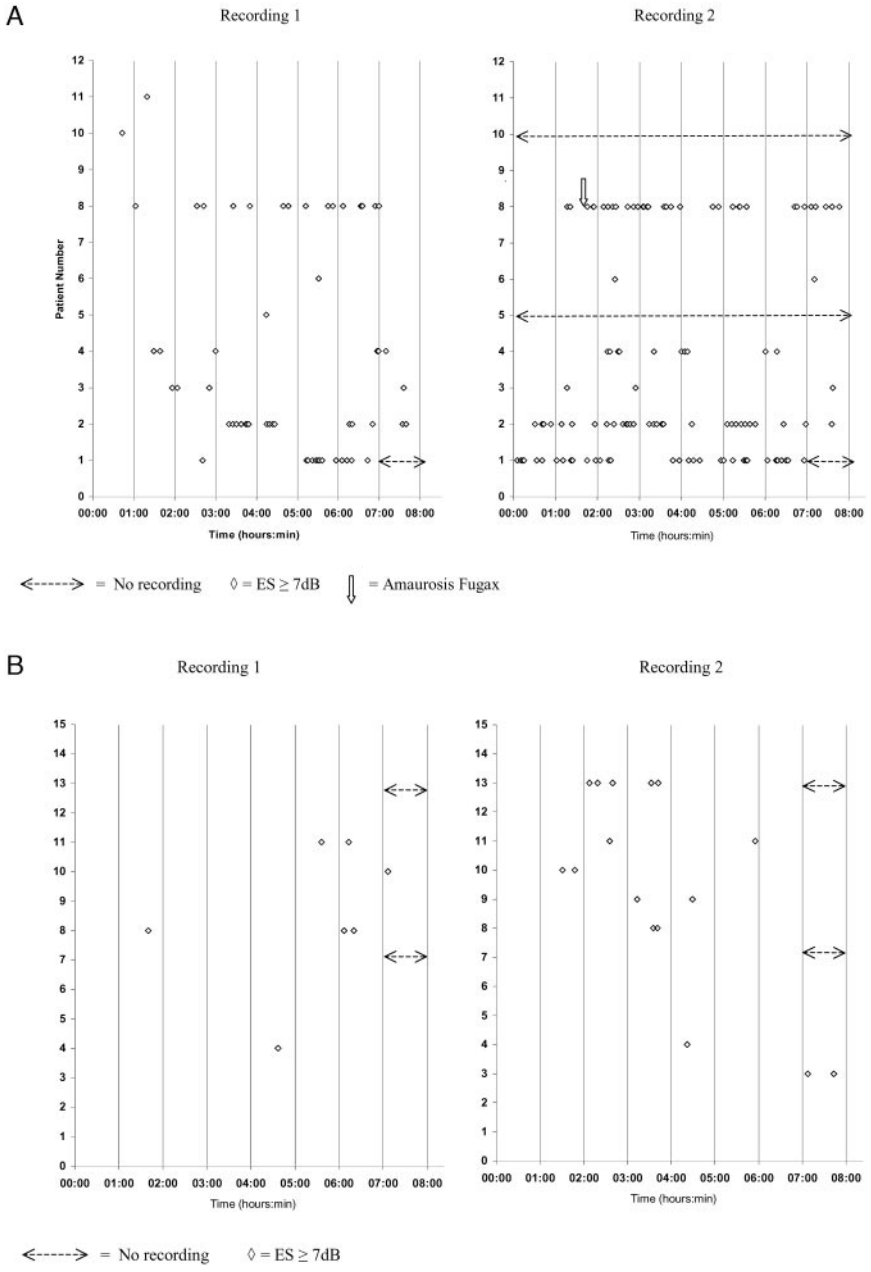
Effect of Repeating and Extending the Recording on the Cumulative Yield

ES were detected in 9 of the 12 (75%) symptomatic subjects. All patients who were ES positive in the recording as a whole had ES in the first 6 hours of first recording (see Table 3). Repeating the recording the following day did not further increase the yield of ES-positive patients. Therefore, 1 recording of 6 hours on either day would have achieved the maximum yield of ES-positive patients. In the asymptomatic subjects, 7 of 15 (46.7%) patients were ES positive on 1 or both recordings. Four (26.7%) had ES on both recordings. After repeating the 8-hour recording 1 week later, the yield of ES-positive patients increased from 26.7% to 46.7% (Table 3).

Comparison Between Different Recording Strategies

The comparison between different recording strategies was assessed using the κ statistic. The greater the κ value, the greater the agreement between the 2 recordings and, therefore, the less informative the second recording. There was excellent agreement between two 8-hour recordings performed on consecutive days in symptomatic patients ($\kappa=0.78$, $P=0.011$). This same level of agreement was achieved for the first 6 hours of each recording ($\kappa=0.78$, $P=0.011$) but not for the first 4 hours of each recording ($\kappa=0.58$, $P=0.065$). For the first recording, there was moderate agreement between the first 4 hours and all 8 hours ($\kappa=0.64$, $P=0.018$). In contrast, for recording 2 there was complete agreement between the first 4 hours and all 8 hours ($\kappa=1.0$, $P=0.002$).

In the asymptomatic group, there was fair agreement between two 8-hour recordings performed 1 week apart ($\kappa=0.59$,



A, Temporal distribution of embolic signals detected in symptomatic carotid stenosis patients during two 8-hour ambulatory TCD recordings. Each point represents a single embolic signal. Patient 8 had amaurosis fugax for 2 minutes during recording 2, indicated by downward arrow. B, Temporal distribution of embolic signals detected in asymptomatic carotid stenosis patients during two 8-hour ambulatory TCD recordings. Each point represents a single embolic signal.

P=0.013). This level of agreement remained for two 6-hour recordings (κ=0.55, P=0.018) but not for two 4-hour recordings, for which there was poor agreement (κ=0.25, P=0.14). For the first recording, there was poor agreement between the first 4 hours and all 8 hours (κ=0.33, P=0.086). In contrast, for recording 2, there was moderate agreement between the first 4 hours and all 8 hours (κ=0.73, P=0.003).

Discussion

This is the first study to apply ambulatory TCD to patients with both symptomatic and asymptomatic carotid stenosis. It shows the prevalence of asymptomatic embolization in patients with the 2 conditions when long recording durations of 8 hours are performed. The results of repeating recordings also provide important information when planning optimal recording protocols in these 2 patient groups.

Determining optimal recording protocols is essential to maximize the detection of ES, while avoiding prolonging the recording duration unnecessarily. Our data suggest that for symptomatic patients, a 6-hour recording on either day would give a maximal yield. In addition, in this group, there was excellent agreement between repeated recordings. This has 2 implications. Firstly, repeating the recording on a second day is of limited benefit in determining the extent to which a patient is embolizing. Secondly, the stability of recordings over time makes this a more powerful situation in which to test therapeutic efficacy. In contrast, in asymptomatic patients, the first 8-hour recording detected embolic signals in 27% of individuals. Repeating the recording on a second occasion increased this proportion to 47%. This reflects a lower rate of embolization and, therefore, increased temporal variability in asymptomatic patients. It may have important implications for applying the

TABLE 3. Increase in Proportion of ES-Positive Patients Resulting From Increasing the Recording Time from One Hour to Sixteen Hours (Recording 1 and 2)

	No. of Positive Recordings (%)	
Time From Start of Recording (h)	Symptomatic Patients	Asymptomatic Patients
Recording 1	(N=12)	(N=15)
1	1 (8.3)	0 (0)
2	5 (50)	1 (6.7)
3	6 (41.7)	1 (6.7)
4	7 (58.3)	1 (6.7)
5	8 (66.7)	2 (13.3)
6	9 (75)	3 (20)
7	9 (75)	3 (20)
8	9 (75)	4 (26.7)
Recording 2	(N=10)	(N=15)
9	9 (75)	4 (26.7)
10	9 (75)	4 (26.7)
11	9 (75)	5 (33.3)
12	9 (75)	6 (40)
13	9 (75)	6 (40)
14	9 (75)	6 (40)
15	9 (75)	6 (40)
16	9 (75)	7 (46.7)

technique to asymptomatic patients. There is interest in the use of the technique to identify a high-risk group of patients with asymptomatic carotid stenosis who may benefit from endarterectomy. However, obtaining a robust and reproducible estimate of embolization in this group may require prolonged recordings on more than 1 occasion.

This study also demonstrates a number of novel features about the pattern of embolization in patients with carotid artery stenosis and, in particular, that embolization is not a random process, but that temporal clustering occurs.

We have compared the proportion of ES-positive hours in the 2 groups with previous studies. The largest study in asymptomatic carotid stenosis is the ongoing Asymptomatic Carotid Emboli Study (ACES).[10] An analysis of patients recruited up to 2002 demonstrated that 53 of 500 hours of recordings (10.6%) were ES positive. This is of the same order as the 16 of 236 (6.8%) hours of recordings in asymptomatic patients in this study. Studies recruiting consecutive symptomatic carotid patients for 1-hour conventional recordings have reported ES in 30% to 45%.[7–9,17,18] In the current study, 55 of 182 (30.2%) hours of recording in the symptomatic group were positive. Therefore, the results of our study are comparable to those from nonambulatory transcranial Doppler, suggesting we studied a similar population, and the technique is detecting a similar number of embolic signals.

In conclusion, our study demonstrates that ambulatory recording for up to 8 hours is possible in patients with carotid artery stenosis. These recordings show the marked temporal variability of embolization. This may be a particular problem in obtaining accurate estimates of stability of asymptomatic carotid plaque. Our study provides baseline data to allow studies in both asymptomatic and symptomatic carotid stenosis to be planned.

Acknowledgments

This study was supported by a grant from the British Heart Foundation (PG 2000083). We thank Prof Dariush Nassiri and Dr Alban Killingback for ultrasound safety testing, Ruth Keating and Katie Weatherstone for embolic signal analysis, and Dr Martin Punter for with patient recordings.

References

1. Siebler M, Kleinschmidt A, Sitzer M, Steinmetz H, Freund HJ. Cerebral microembolism in symptomatic and asymptomatic high-grade internal carotid artery stenosis. *Neurology*. 1994;44:615–618.
2. Markus HS, Thomson ND, Brown MM. Asymptomatic cerebral embolic signals in symptomatic and asymptomatic carotid artery disease. *Brain*. 1995; 118:1005–1011.
3. Van Zuilen EV, Moll FL, Vermeulen FE, Mauser HW, van Gijn J, Ackerstaff RG. Detection of cerebral microemboli by means of transcranial Doppler monitoring before and after carotid endarterectomy. *Stroke*. 1995;26: 210–213.
4. Siebler M, Sitzer M, Rose G, Bendfeldt D, Steinmetz H. Silent cerebral embolism caused by neurologically symptomatic high-grade carotid stenosis. Event rates before and after carotid endarterectomy. *Brain*. 1993;116: 1005–1015.
5. Sitzer M, Muller W, Siebler M, Hort W, Kniemeyer HW, Jancke L, Steinmetz H. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. *Stroke*. 1995;26:1231–1233.
6. Valton L, Larrue V, Arrue P, Geraud G, Bes A. Asymptomatic cerebral embolic signals in patients with carotid stenosis. Correlation with appearance of plaque ulceration on angiography. *Stroke*. 1995;26:813–815.
7. Markus HS, Mackinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005;36:971–975
8. Valton L, Larrue V, le Traon AP, Massabuau P, Geraud G. Microembolic signals and risk of early recurrence in patients with stroke or transient ischemic attack. *Stroke*. 1998;29:2125–2128.
9. Censori B, Partziguian T, Casto L, Camerlingo M, Mamoli A. Doppler microembolic signals predict ischemic recurrences in symptomatic carotid stenosis. *Acta Neurol Scand*. 2000;101:327–331.
10. Major Ongoing Stroke Trials. The Asymptomatic Carotid Emboli Study (ACES). *Stroke*. 2002;33:1729.
11. Kaposzta Z, Martin JF, Markus HS. Switching off embolization from symptomatic carotid plaque using S-nitrosoglutathione. *Circulation*. 2002;105: 1480–1484.
12. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, Goodhall AH, Naylor AR. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation*. 2004;109:1476–1481.
13. Mackinnon AD, Aaslid R, Markus HS. Long-term ambulatory monitoring for cerebral emboli using transcranial Doppler ultrasound. *Stroke*. 2004;35: 73–78.
14. Bluth EI, Stavros AT, Marich KW, Wetzner SM, Aufrichtig D, Baker JD. Carotid duplex sonography: a multicenter recommendation for standardized imaging and Doppler criteria. *Radiographics*. 1988;8:487–506.
15. Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke*. 1998;29:725–729.
16. Markus H, Bland JM, Rose G, Sitzer M, Siebler M. How good is intercenter agreement in the identification of embolic signals in carotid artery disease? *Stroke*. 1996;27:1249–1252.
17. Droste DW, Dittrich R, Kemeny V, Schulte-Altedorneburg G, Ringelstein EB. Prevalence and frequency of microembolic signals in 105 patients with extracranial carotid artery occlusive disease. *J Neurol Neurosurg Psychiatry*. 1999;67:525–528.
18. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 1999;30:1440–1443.