

# Long-Term Ambulatory Monitoring for Cerebral Emboli Using Transcranial Doppler Ultrasound

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

**Background and Purpose**—Transcranial Doppler (TCD) monitoring for asymptomatic cerebral emboli is currently limited to short recordings by equipment size, restricting its clinical usefulness. We have developed a first ambulatory TCD system, evaluated it in at-risk patient groups, and used it to study the pattern of embolization in patients with symptomatic carotid stenosis.

**Methods**—The system comprises an 18×11.5×3.2 cm battery-powered Doppler unit (425 g) and a 13-mm servo-controlled 2 MHz transducer probe. The quadrature raw Doppler signal is stored on flash-disk. An autosearch algorithm restores vessel insonation should signal quality fall. Initial evaluation was in 20 ambulatory stroke patients. Subsequently, 12 recently symptomatic carotid patients had recordings for ≥5 hours.

**Results**—Recordings were well tolerated and a median of 96% of Doppler signal was suitable for analysis. Embolic signals were detected in 11 of the 12 symptomatic carotid patients. There was marked temporal variability in embolization and prolonging the recording increased the yield of embolic signal positive patients from 58% at 30 minutes to 92% at 150 minutes. In 3 subjects with frequent embolic signals, significant temporal clustering of embolic signals was observed.

**Conclusions**—We have developed the first ambulatory TCD system. Good-quality recordings of ≥5 hours can be obtained. In view of the demonstrated temporal variability in embolization, this technique is likely to improve the predictive value of recording for asymptomatic embolic signals and may be particularly useful in patients in whom embolic signals are relatively infrequent, such as those with asymptomatic carotid stenosis and atrial fibrillation. (*Stroke*. 2004;35:73-78.)

**Key Words:** carotid stenosis ■ cerebral embolism ■ stroke ■ ultrasonography, Doppler, transcranial

The use of Doppler ultrasound to estimate blood flow velocity was described in 1960.<sup>1</sup> In the 1980s it was appreciated that sufficient ultrasound would pass through the skull to allow detection of blood flow within the intracranial circulation.<sup>2</sup> Since then, transcranial Doppler (TCD) ultrasound has been put to a variety of uses including detection of intracranial stenoses, intraoperative monitoring, measurement of dynamic cerebrovascular responses, and embolic signal detection.<sup>3</sup>

Over the past decade, TCD has been used to detect and monitor asymptomatic emboli in patients with a variety of cardiovascular diseases. These asymptomatic embolic signals are considerably more frequent than clinical embolic events.<sup>4</sup> Animal and in vitro studies have shown the technique to be both sensitive and specific in the detection of emboli.<sup>5,6</sup> There is increasing evidence that asymptomatic embolic signals, particularly in patients with carotid artery stenosis, are an independent risk factor for transient ischemic attack and stroke.<sup>7-9</sup> TCD may have application in selecting high-risk groups for particular surgical or pharmacological therapies and as a surrogate marker for evaluating new antiplatelet and

anticoagulant therapies.<sup>4</sup> However, embolization is a dynamic process and may show marked temporal variability when short recordings of 30 to 60 minutes are performed,<sup>10</sup> as is usually the case with current nonportable equipment. In addition, in many conditions, such as atrial fibrillation, embolic signals are infrequent and may not occur during recordings periods of 1 hour.<sup>11</sup> Prolonging recordings is likely to increase the yield of embolic signal-positive patients and reduce variability within patients. By allowing a more reliable estimate of the presence and frequency of embolization, one might expect an improved correlation between Doppler embolic signals and clinical outcome.

The current technique utilizes nonportable or barely portable equipment, requiring the patient to be stationary during the recording period. Although prolonged recordings have previously been performed in 7 patients with a conventional system,<sup>12</sup> the nonportability makes this impractical for clinical use, and recording duration is limited to a maximum of 1 hour. In order to perform prolonged clinical recordings, the patient needs to be ambulatory. An ambulatory system requires a small, easily portable Doppler unit, a method of

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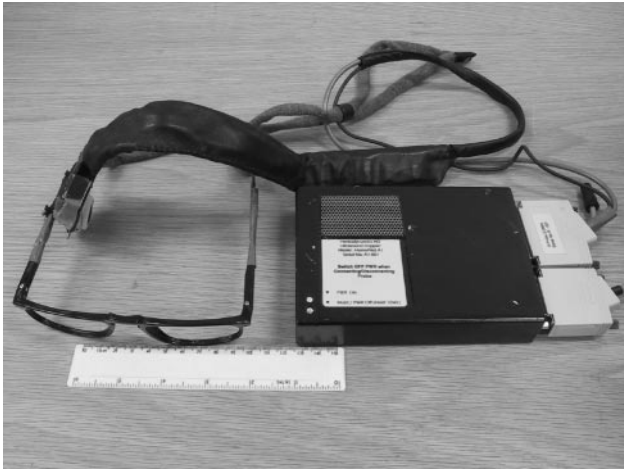
From the Department of Clinical Neurosciences (A.D.M., H.S.M.), St. George's Hospital Medical School, London, UK; and Hemodynamics AG (R.A.), Bern, Switzerland.

Correspondence to Prof Hugh Markus, Dept of Clinical Neurosciences, St. George's Hospital Medical School, Cranmer Terr, Tooting, London SW17 0RE, UK. E-mail- hmarkus@sghms.ac.uk

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**Figure 1.** The ambulatory transcranial Doppler apparatus.

data storage, a long-life battery pack, and a means of transducer fixation and control that is comfortable and acceptable to the patient.

We have developed an ambulatory TCD system. The aims of this study were to demonstrate that continuous prolonged TCD recordings can be performed in ambulatory stroke patients and to apply the technique to patients with a potential cerebral embolic source, symptomatic carotid stenosis.

## Methods

### Equipment Design and Set-Up

The system is illustrated in Figure 1. The physical design is rugged and lightweight. The battery-powered Doppler unit is enclosed in a rigid aluminum shell with approximate dimensions of 18×11.5×2.4 cm and weighing 425 g. The unit has an inbuilt loudspeaker and a solid-state flash disk for storage of the quadrature raw Doppler signal. 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. The probe has a lightweight protective cover (Figure 1) for mechanical shielding and cosmetic purposes. The Doppler unit has a dynamic range of 60 dB. Prior to performing ambulatory recordings, the unit was tested and shown to have the same or better sensitivity than current trolley-based TCD instruments.

### Software and Data Acquisition

The quadrature raw audio signal is sampled and converted using a 12-bit A/D conversion. The digitized samples are compressed using a no-loss algorithm. The compressed data are stored on a M-Systems flash-disk of 288 MB capacity. The software monitors the Doppler signal quality and has an auto-search module that attempts to restore the vessel insonation during recording when the signal drops below a preset level. Moreover, at intervals of about 5 minutes the search mode is activated to optimize insonation. After the recording, the data can be transferred from the flash-disk to the PC-based computer.

### Safety Considerations

Ultrasound safety testing was performed with the Bath radiation force balance and a bilaminar membrane hydrophone. The output power of the TCD machine is limited to 50 mW equating to a thermal cranial index (TIC) of 0.8. American Institute of Ultrasound in Medicine (AIUM) and British Medical Ultrasound Society (BMUS) recommend limiting the TIC to <2.0.<sup>13,14</sup> The maximum on axis peak rarefaction pressure  $P_{-ve}$  was 0.295 MPa yielding a mechanical index of 0.21, which is well within BMUS safety guidelines. The spatial-peak-temporal-average ultrasonic intensity of the unit is



**Figure 2.** A patient during an ambulatory TCD recording; the transducer is held in place on a glasses frame.

restricted to a level of 100 mW/cm<sup>2</sup>, which is considered safe for prolonged exposure, according to AIUM recommendations.<sup>15</sup>

Three independent mechanisms limit the amount of power generated. First, failure of the computer, or Doppler, automatically shuts down the power supply for the burst amplifier. Second, the burst amplifier automatically limits the power to specific levels. Third, the software program used to control the power setting during the initial set-up limits the operator to using a power <50 mW and axial sample volume <10 mm.

### Set-Up

The middle cerebral artery (MCA) Doppler signal is obtained via the transtemporal window with a conventional Doppler unit (Pioneer 4040 with 2 MHz transducer, Nicolet/EME Ltd). Then the ambulatory probe is positioned at the location where the transtemporal ultrasound window is found. Set-up and control of the ambulatory module are performed via a laptop computer connected by a serial port. During set-up, the Doppler spectrum is viewed in real time on the laptop and all functions and settings of the Doppler unit are remotely controlled and stored. When the MCA signal is found, its strength is optimized using the autosearch software module. The unit is then disconnected from the laptop and placed in the pocket of a jacket worn by the patient. Recording continues with unchanged Doppler settings until the unit is powered off or the flash-disk is filled to capacity.

### System Evaluation

The system was first evaluated in a cohort of stroke patients and then applied to a group of patients with a potential embolic source, symptomatic carotid stenosis.

### Initial Evaluation

Consecutive patients admitted to the acute stroke unit were recruited. Selection criteria were (1) cognitive, visual, and motor skills, allowing documentation of the patient's own activities during the recording; (2) ambulatory, defined as the ability to walk a few steps, with a walking aid if required; (3) an acoustic window allowing TCD recording with a conventional TCD system; (4) an MCA signal obtainable with a power of <50 mW; and (5) ability to provide informed consent. When the stroke was in the MCA territory, recordings were made preferentially from the symptomatic MCA. All patients gave informed written consent and the project was approved by the local research ethics committee.

During the recording, patients were either ambulatory on the ward or attending physiotherapy and occupational therapy. They were asked to continue their activities as usual. The operator visited the patient hourly and manual adjustments were made if the audio signal was perceived to be weak or absent.

TABLE 1. Subject and Recording Details

	All Patients (n=20)	Headband Transducer Fixation (n=10)	Glasses Transducer Fixation (n=10)	P Value (Mann-Whitney)
Age, median (range)	66 (38–91)	71 (56–88)	61 (38–91)	0.160
Male	11	6	5	0.661
Side of MCA insonated				
Left	8	5	3	0.374
Right	12	5	7	
Set-up time				
0–30 min	16	7	9	0.234
30–60 min	0	0	0	
60–90 min	2	1	1	
>2 h	2	2	0	
Median (range) ambulatory time, min	340 (325–385)	329.5 (325–385)	343 (330–362)	0.074
Median (range) MCA Doppler signal, min	304 (190–326)	297 (190–326)	308 (223–325)	0.257
Median (range) MCA Doppler signal, % of recording	96 (58–100)	91 (58–100)	98 (86–100)	0.099
Median (range) recording quality*	3.0 (2.0–4.0)	2.0 (2.0–4.0)	3.75 (2.0–4.0)	0.024
No. of manual adjustments required	20	18	2	0.004
Headache	3	3	0	0.067

MCA indicates middle cerebral artery.

\*4=very good; 3=good; 2=fair; 1=poor.

Both a proprietary elastic headband and glasses (Figure 2) were initially evaluated as methods of probe fixation. For each patient the following parameters were recorded: (1) method of transducer fixation: glasses or headband; (2) side of insonation; (3) set-up duration; (4) ambulatory duration (total time patient wore the apparatus); (5) total file recording duration; (6) MCA signal recording duration, calculated using an overall summary curve of mean MCA velocities (Figure 3); (7) file recording quality; (8) number of manual adjustments per recording; (9) Doppler settings (MCA side, depth, sample volume, power, gain, pulse repetition frequency, servo position of probe) and (10) side effects. For each subject, both the total duration of recording and the duration during which recordings of sufficient quality for clinical interpretation were obtained were determined. File recording quality was determined by an independent assessor, blinded to the clinical details and experienced in the field of TCD. For each recording, sample spectra were analyzed for quality at 30-minute intervals (ie, 10 samples in a 5-hour recording). The spectra were rated into 4 categories: (1) absent/poor signal; (2) fair signal; (3) good signal; and (4) very good signal, based on predetermined color thresholds. For each recording the median file quality score was calculated and subsequently the median file quality score for each subgroup (glasses or headband) was determined. Comparisons were made between the glasses and headband fixation groups using Mann-Whitney *U* test.

#### Application to Carotid Stenosis

Twelve consecutive patients with  $\geq 50\%$  symptomatic internal carotid stenosis were recruited for 1 ambulatory recording  $\geq 5$  hours. Mean (SD, range) stenosis was 85.7 (15.2, 50% to 99%). Symptomatic was defined as having symptoms (amaurosis fugax, transient ischemic attack, or stroke) in the territory of the stenosed carotid artery in the preceding 3 months. For all subjects the glasses method of fixation was used.

All embolic signal analysis was performed blind to individual patient details and the hour of recording. If the recording extended beyond 5 hours, the first 5 hours were analyzed. Embolic signals (ES) were identified using International Consensus Criteria by their typical visual appearance on the spectral display and their characteristic sound.<sup>16</sup> In addition, an intensity threshold of  $\geq 7$  dB was

used because this has been shown to increase interobserver agreement.<sup>17</sup> To examine the temporal pattern of embolization and whether clustering occurred, for each patient the time interval between successive ES was calculated. For patients with frequent ES, the distribution of time intervals was compared with the normal distribution by plotting a normal Q-Q plot and using the Shapiro-Wilk test.

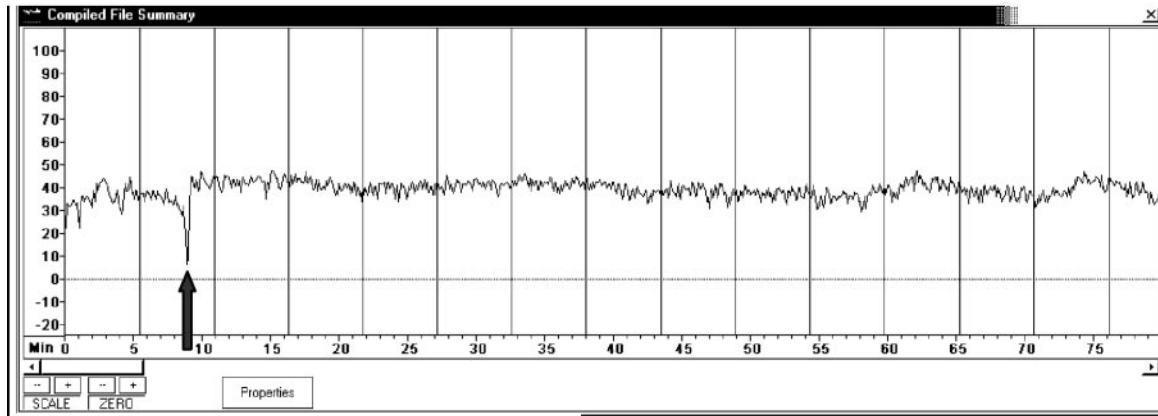
## Results

### Initial Evaluation

Twenty-four consecutive patients were recruited. Three had no transtemporal ultrasound window detected using the conventional TCD system. One patient had successful conventional TCD recordings, but fixation of the ambulatory transducer could not be successfully maintained. For the remaining 20 patients in whom ambulatory TCD recordings could be performed, results are given in Table 1. Figure 3 shows a summary curve of mean MCA velocities from one of the recordings.

Transducer fixation was with headband in 10 patients and glasses in 10. Median ambulatory duration was 5 hours 40 minutes (range, 5 hours 25 minutes to 6 hours 25 minutes). The maximum available capacity of the current size flash-disk was between 5 hours and 5 hours 40 minutes, depending on signal strength with higher audio amplitudes requiring more disk space. From the data recorded onto flash-disk, the median time an MCA Doppler signal was achieved was 5 hours 4 minutes, equating to a median of 96% of available file recording time.

Fixing the transducer in place with the glasses resulted in recordings of better quality, and fewer manual adjustments were required compared with fixation with the headband. There were no complaints of discomfort with the glasses,



**Figure 3.** Summary curve of mean middle cerebral artery velocities (cm/s) during the first 75 minutes of a 5.5-hour recording. At 8 minutes (black arrow), the autosearch algorithm recognizes the weak signal and self adjusts. The signal is restored.

whereas 3 of the 10 patients using the headband complained of a mild temporary headache due to pressure from the band (Table 1). Therefore, the glasses were used for transducer fixation for the subsequent study below.

During the study, no patient suffered temporary or permanent skin damage. There were no side effects that resulted in the monitoring procedure having to be curtailed. Patients successfully continued with their usual activities on the ward and also attended their scheduled physiotherapy or occupational therapy, wearing the apparatus.

### Application to Carotid Stenosis

Ambulatory TCD recordings were possible in all 12 patients. In patients 3, 4, and 5, although they were ambulatory with the equipment for >5 hours, the file recording length was limited to 4 hours 35 minutes due to a software problem, which was corrected for the subsequent patients.

ES were detected in 11 of the 12 symptomatic carotid patients. Of 58.9 hours recording, 28 hours (48%) were ES-negative (Table 2). In 3 patients (4, 6, 11), ES were

detected in every complete hour of the 5-hour recording. These 3 patients had the highest total ES load (36, 24, and 29, respectively). The effect of extending the recording time on the yield of ES-positive patients was determined. The proportion of patients who were ES-positive was 58% at 1 hour, 83% at 2 hours, and 92% at 150 minutes. It did not increase with further duration of recording.

The scatter plot data (Figure 4) demonstrates the temporal variability of ES. In patients with high embolic load (patients 4, 6, and 11), there appeared to be temporal clustering of ES with  $\geq 5$  ES occurring in a 15-minute period and sometimes within 5 minutes. For these patients, time intervals between successive ES were not normally distributed, with a skew to short time intervals, demonstrating that embolization is a nonrandom process. The Shapiro-Wilk test confirmed significant deviation from the normal distribution ( $P=0.01$ ).

### Discussion

This study describes the first evaluation of an ambulatory TCD system. We have demonstrated that prolonged ambulatory recordings can be successfully performed and that the technique is applicable to cerebral embolic signal monitoring where it gives new information on the pattern of cerebral embolization.

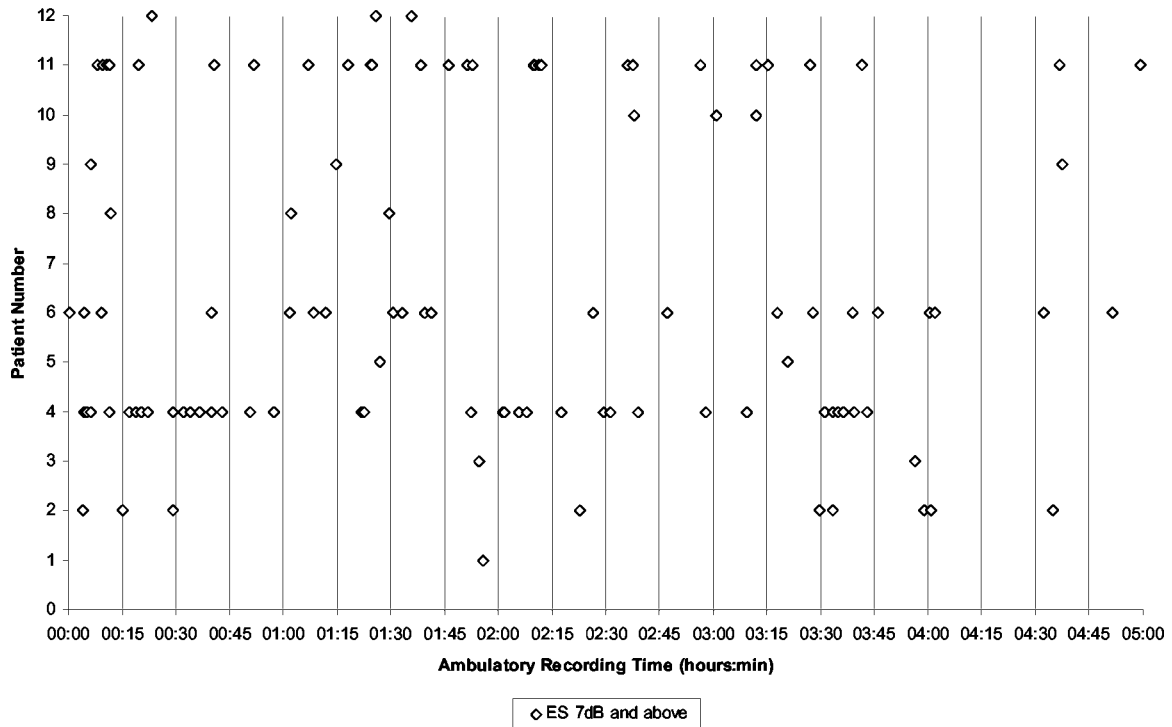
The system has several features that allow for optimal recordings. The instrument is small and lightweight, fitting neatly into a jacket pocket. This allowed patients to continue daily activities without interrupting recordings. The autosearch facility aids initial set-up and searches at regular intervals during the recording, self-adjusting should the signal quality fall. Most importantly, this feature allowed the MCA Doppler signal to be maintained for 96% to 98% of the possible recording time. The small size and light weight of the probe contributed to the stability of the transducer fixation. Using a glasses method of probe fixation, we achieved prolonged recordings with minimal or no discomfort.

These prolonged recordings for cerebral ES in patients with carotid stenosis reveal a number of important, and novel, insights into the pattern of cerebral embolization. First, if prolonged recordings are performed, almost all patients were found to have some embolic signals. This is consistent with

**TABLE 2. Embolic Signals Detected in Symptomatic Carotid Stenosis Patients During Each Hour of Recording**

Patient No.	Recording Time (hr:min)	Embolic Signals per Hour					Total ES
		H1	H2	H3	H4	H5	
1	05:00	0	1	0	0	0	1
2	05:00	3	0	1	3	2	9
3	04:36	0	1	0	1	0	2
4	04:37	16	4	9	7	0	36
5	04:41	0	1	0	1	0	2
6	05:00	4	9	2	5	4	24
7	05:00	0	0	0	0	0	0
8	05:00	1	2	0	0	0	3
9	05:00	1	1	0	0	1	3
10	05:00	0	0	1	2	0	3
11	05:00	7	8	8	4	2	29
12	05:00	1	2	0	0	0	3
Total	58:54	33	29	21	23	9	115

H indicates hour; ES, embolic signals.



**Figure 4.** The temporal distribution of embolic signals detected in symptomatic carotid stenosis patients during 5-hour ambulatory TCD recording. Each point represents a single embolic signal.

previous studies in which recording times were prolonged up to 3 hours using conventional TCD equipment.<sup>18</sup> This emphasizes the dynamic nature of cerebral embolization, which is not a one-to-one phenomenon between embolus and symptoms. Performing prolonged recordings may allow better investigation of factors that determine whether emboli result in symptoms. Second, there is considerable temporal variability in the pattern of embolization and this may influence results if only short-duration recordings are performed; implications of this are discussed below. Third, we have shown for the first time that the pattern of embolization is not random but exhibits temporal clustering.

It is likely that prolonged ambulatory TCD recordings will have a number of potential clinical applications both for cerebral emboli detection and monitoring cerebral hemodynamics. We have shown that prolonging recordings is likely to provide a better estimate of overall embolic load and therefore reducing interpatient variability. This may increase the predictive value of recording for asymptomatic emboli. It may also improve the use of the technique when evaluating novel therapies in small groups of patients<sup>19</sup> and in evaluating the effectiveness of antiplatelet and anticoagulant therapy in individual patients. 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 current gold standard for emboli detection is the human expert and this is very time-consuming. It will therefore be essential to develop an automated embolic signal detection system for evaluation of prolonged recordings. Recently available commercial systems have been found to

have much improved performance at least in patients with emboli from symptomatic carotid stenosis or after carotid endarterectomy.<sup>20</sup>

There have been concerns about prolonged ultrasound exposure and we have addressed this issue. Laboratory testing prior to patient recordings showed that the instrument met both AIUM and BMUS recommendations.<sup>13-15</sup>

In conclusion, we have developed a first ambulatory TCD system and have overcome the problem of prolonged transducer fixation. We have demonstrated that ambulatory acute stroke patients tolerate recordings of 5 to 6 hours well and that in the majority these recordings were of good quality. These findings are encouraging but further studies are required in those ethnic groups and the very elderly in whom temporal ultrasound windows may be less optimal. The system has allowed prolonged assessment of embolic signals in patients with symptomatic carotid stenosis, demonstrating temporal variability. Longer recordings may be useful in the evaluation of embolization in patients with a predicted low but positive emboli yield, such as those with asymptomatic carotid stenosis and atrial fibrillation. Imminent developments, with improvements in data storage and battery capacity, should allow recording to be increased to beyond 8 hours in the near future.

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## References

1. Satomura S, Kaneko Z. Ultrasonic blood rheograph. Proceedings of the 3rd International Conference on Medical Electronics. 1960;254–258.
2. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg.* 1982;57:769–774.
3. Markus HS. Transcranial Doppler ultrasound. *Br Med Bull.* 2000;56:378–388.
4. Markus H. Monitoring embolism in real time. *Circulation.* 2000;102:826–828.
5. Russell D, Madden KP, Clark WM, Sandset PM, Zivin JA. Detection of arterial emboli using Doppler ultrasound in rabbits. *Stroke.* 1991;22:253–258.
6. Markus HS, Brown MM. Differentiation between different pathological cerebral embolic materials using transcranial Doppler in an in vitro model. *Stroke.* 1993;24:1–5.
7. Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J, Steinmetz H. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. *Stroke.* 1995;26:2184–2186.
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. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke.* 1999;30:1440–1443.
10. Molloy J, Khan N, Markus HS. Temporal variability of asymptomatic embolization in carotid artery stenosis and optimal recording protocols. *Stroke.* 1998;29:1129–1132.
11. Cullinane M, Wainwright R, Brown A, Monaghan M, Markus HS. Asymptomatic embolization in subjects with atrial fibrillation not taking anticoagulants: a prospective study. *Stroke.* 1998;29:1810–1815.
12. Droste DW, Decker W, Siemens HJ, Kaps M, Schulte-Altdorferburg. Variability in occurrence of embolic signals in long term transcranial Doppler recordings. *Neurol Res.* 1996;18:25–30.
13. American Institute of Ultrasound in Medicine (AIUM) 40th annual convention. New York, NY, March 17–20, 1996. Abstracts. *J Ultrasound Med.* 1996;15:S1–S117.
14. Abstracts from the 13th EUROSON Congress, 33rd BMUS Annual Meeting, Edinburgh, Scotland, December 11–14, 2001. *Eur J Ultrasound.* 2002;15:S1–S60.
15. Bioeffects considerations for the safety of diagnostic ultrasound. American Institute of Ultrasound in Medicine. Bioeffects Committee. *J Ultrasound Med.* 1988;7:S1–S38.
16. 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.
17. 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.
18. 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.
19. Kaposzta Z, Martin JF, Markus HS. Switching off embolization from symptomatic carotid plaque using S-nitrosoglutathione. *Circulation.* 2002;105:1480–1484.
20. Cullinane M, Reid G, Dittrich R, Kaposzta Z, Ackerstaff R, Babikian V, Droste DW, Grosset D, Siebler M, Valton L, Markus HS. Evaluation of a new on-line automated embolic signal detection algorithm, including comparison with a panel of international experts. *Stroke.* 2000;31:1335–1341.