

Automatic Online Embolus Detection and Artifact Rejection With the First Multifrequency Transcranial Doppler

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Background and Purpose—The goal of this study was to assess the first multifrequency transcranial Doppler system specially developed for online automatic detection of cerebral microemboli.

Methods—The multifrequency Doppler instrumentation insonates simultaneously with 2.0- and 2.5-MHz frequencies. The detection threshold for embolus detection used in this study was a relative Doppler energy increase of >20 dB · ms, at which point the Doppler power increase was at least 5 dB and lasted >4 ms above the background energy. Four parameters were used in an optimized binary decision tree to recognize emboli: quarter Doppler shift, maximum duration limit, reference gate, and bidirectional enhancement. In vitro studies, 200 plastic microspheres (80 μ m), 200 gas bubbles (8 to 25 μ m), and 600 artifacts were studied in a pulsatile closed-loop system. In vivo studies were carried out for 1 hour in 15 patients with mechanical heart valves and in 45 patients with carotid stenosis. This gave a total of 60 hours of online automatic monitoring in patients.

Results—All 400 plastic spheres and microbubbles were automatically detected and correctly classified. Of the 600 artifacts, 596 (99.3%) were correctly classified as artifacts, and 4 (0.7%) were incorrectly identified as emboli ($\kappa=0.992$, $P<0.001$). The experienced observer detected a total of 554 emboli and 800 artifacts in the heart valve (521 emboli, 400 artifacts) and carotid stenosis (33 emboli, 400 artifacts) patients. With multifrequency Doppler, 546 of these emboli (98.6%) and 791 of these artifacts (98.9%) were automatically detected and correctly classified as embolus or artifact ($\kappa=0.953$, $P<0.0001$).

Conclusions—We found that multifrequency transcranial Doppler had a relatively high sensitivity and specificity when used to automatically detect cerebral microemboli and reject artifacts online. (*Stroke*. 2002;33:1969-1974.)

Key Words: carotid stenosis ■ cerebral embolism ■ mechanical heart valve prostheses ■ ultrasonography, Doppler

Transcranial Doppler ultrasound (TCD) may be used to detect cerebral microemboli in several groups of patients who have increased stroke risk¹⁻⁴ and during invasive cardiovascular investigations and operations.⁵⁻¹⁰ However, although this method was described >10 years ago,^{11,12} it has not yet reached its potential in routine clinical practice, primarily because we do not have an automatic online embolus detection system that has been shown to detect and classify microemboli with the required sensitivity and specificity. The human observer is currently used as the “gold standard” not because of accuracy but rather because there has been no better alternative. The personal assessment of TCD monitoring for microemboli is also very time consuming and therefore not suitable for clinical use. These reasons may explain the discrepancies reported in the literature on the prevalence and frequency of microembolic signals in various types of stroke or stroke-prone patients.^{1,3,4,13,14}

Cerebral microemboli may be detected by TCD because they cause an increase in reflected Doppler energy, which is the product of a relative Doppler power increase and its duration. However, there are also random energy changes in

the normal Doppler signal resulting from Doppler speckle (random clustering of red blood cells) and during systole compared with diastole. Another difficulty is the fact that artifacts caused, for example, by probe or tissue movements cause an increase in Doppler energy. An automatic embolus detection system must therefore be sensitive enough to detect the smaller solid microemboli that cause small increases in Doppler energy and specific enough to reject Doppler speckle. Second, it must have the ability to determine whether an energy increase is due to an embolus or an artifact.

The aim of this study was to assess in vitro and in vivo studies the first multifrequency TCD system that was specially developed for the online automatic detection of cerebral microemboli.

Materials and Methods

The multifrequency Doppler instrumentation (EmboDop, DWL) insonates simultaneously with 2.0- and 2.5-MHz frequencies. It has a 128 Fast Fourier Transform (FFT) with 60% overlapping and Blackman time-weighted function. It has also a second 2.0-MHz gate that can be used as a reference gate.

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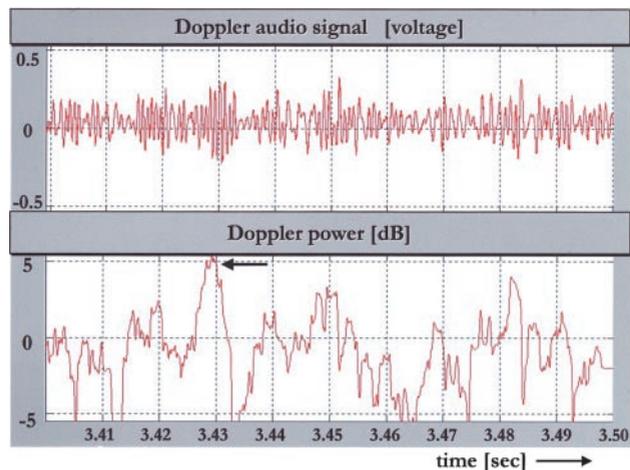


Figure 1. Doppler audio signals (top) and power measurements (bottom) from the MCA of a healthy subject. Normal Doppler speckle may cause relative power increases of >5 dB (arrow).

The 2.0- and 2.5-MHz probes are sensitive wide-frequency band transducers for transcranial application. Embolus monitoring with this system can be carried out bilaterally with 3 Doppler channels on each side. Data may be continuously recorded on the computer hard disk for up to 4 hours with the possibility of transferral to the archive system.

Doppler Power Estimations and Time Window

Short-term power measurements are carried out every 2 ms on the basis of digital root-mean-square calculations.¹⁵ This estimates the average Doppler power with 2-ms time windows using autocorrelation techniques in the time domain. These are used to calculate a moving average of the Doppler power over 30 ms, which is updated every 2 ms. These measurements are used to detect high-energy signals and to exclude normal variations in Doppler energy resulting from Doppler speckle (Figure 1). High-energy signals were defined in this study as relative energy increases of >20 dB · ms, at which point the Doppler power increase is at least 5 dB and lasts >4 ms above the average background energy.

Embolus or Artifact Recognition

After the automatic detection of a high-energy signal, the Doppler instrumentation uses the following 4 parameters to automatically determine whether it is due to an embolus or an artifact.

Quarter Doppler Shift

The quarter Doppler shift is a new parameter for embolus detection that is dependent on the Doppler principle that states that $\Delta f = Ft(V/C)\cos\theta$, where Δf is the Doppler shift frequency, F_t is the transmitting frequency, V is the velocity of the embolus, C is the velocity of sound in blood, and θ is the angle of insonation. Emboli show quarter Doppler shift characteristics when insonated simultaneously with 2.0- and 2.5-MHz frequencies according to the Doppler formula. The Doppler shift frequency caused by an embolus moving through the vessel is therefore one quarter greater (1.25 kHz) with 2.5-MHz insonation compared with that (1.0 kHz) with 2.0-MHz insonation frequency (Figure 2). On the other hand, artifacts may show several peak intensities, but they do not normally show a quarter Doppler shift.

Maximum Duration Limit

The maximum duration limit is the maximum time it would take an embolus to travel through the sample volume under study. The duration of a detected high-energy signal can therefore not exceed this duration limit if it is due to an embolus. This is calculated from the maximum non-angle-corrected velocity at the highest intensity and the sample volume, which is 10 mm (Figure 3). The latter is

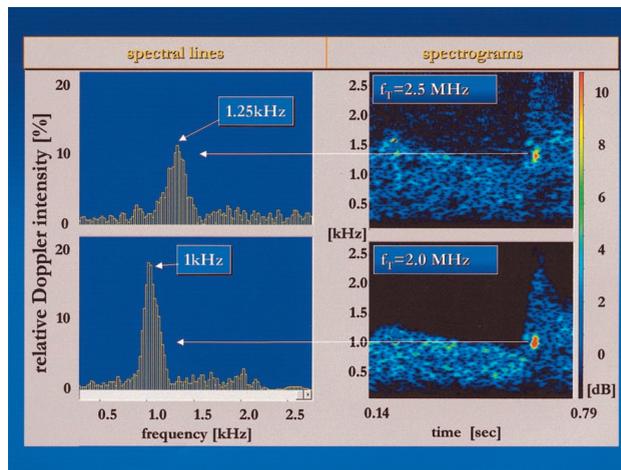


Figure 2. Spectrograms (right) and spectral lines (left) of an MCA embolus insonated by 2.5 and 2.0 MHz. Frequency of the reflected Doppler signal is one quarter greater (1.25 kHz) with 2.5-MHz insonation frequency than that (1.0 kHz) at 2.0-MHz insonation frequency.

lengthened for high-intensity signals by 1 mm for each decibel above 10 dB to compensate for side slopes and the teardrop shape of the sample volume.¹⁶

Reference Gate

This information is obtained by use of a second sample volume not necessarily in the vessel but at a distance at least 10 mm from the sample volume placed in the vessel under study.¹⁷ In clinical monitoring of the middle cerebral artery (MCA), for example, the reference gate should be located close to the temporal bone at a depth of ≈ 30 to 40 mm. An artifact will be detected in both gates at the same time or with a time delay of <4 ms. An embolus will not be detected in the reference gate at all or, if so, with a delay of ≥ 4 ms (Figure 4).

Bidirectional Enhancement

The last parameter is the observation that artifacts normally cause bidirectional enhancement of the Doppler power.^{17,18} This is due to fast vibrations of the transducer or tissues, which cause signal enhancement in the Doppler spectrogram, which is simultaneous in

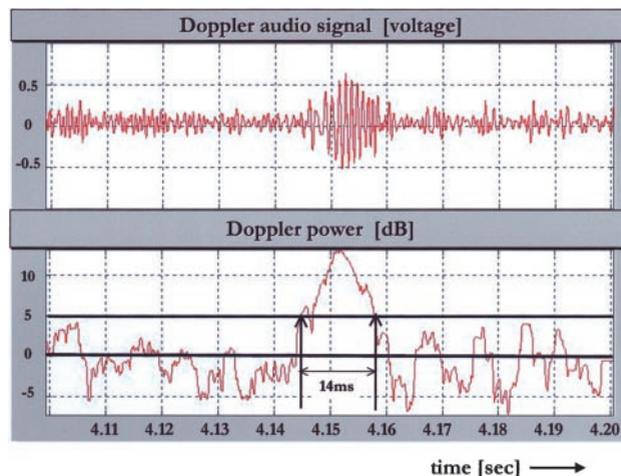


Figure 3. Relative increase in Doppler power (>5 dB) caused by this MCA embolus lasted for 14 ms (arrows). Calculated upper duration limit for an embolus in this sample volume was 25 ms. Shown are audio signals (top) and power measurements (bottom).

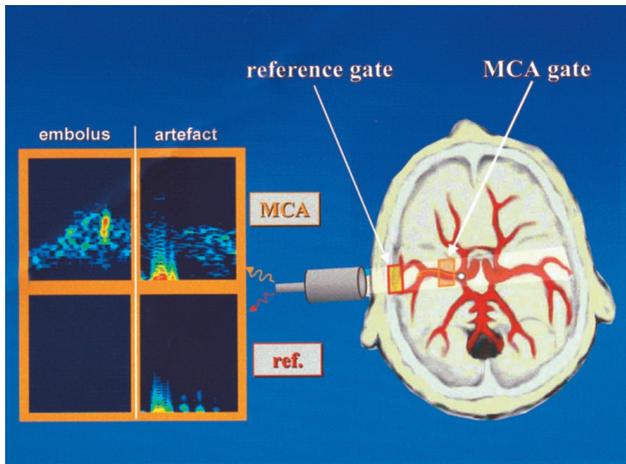


Figure 4. Artifact is seen simultaneously in both the MCA and reference (ref) gates, whereas the embolus is seen only in the MCA gate.

both positive and negative directions. The limits for backward flow enhancement were set at 50% to 150% of that measured in forward flow for artifact recognition.

Binary Decision Tree

The 4 parameters described above are finally analyzed with an optimized binary decision tree that has an automatic Boolean yes or no decision (Figure 5). Optimization had been accomplished before this study by exposing the decision tree to the above parameters of many different embolic signals and artifacts. After the last decision, each high-energy signal was given the final classification assessment of embolus or artifact.

In Vitro Studies

The in vitro studies were carried out with a pulsatile closed-loop system. The silicone tubing had a 3-mm diameter and was immersed in a water tank in which the water temperature was kept constant at 35°C. The background Doppler signal was due to 95% volume fraction distilled water and a 5% volume fraction of 5- to 20-μm particles of iridium-302 Pearl Luster Pigment Powder (Merck Co) for half of the studies and heparinized pig blood for the remainder. The tubing was insonated through Plexiglas damping layers at a 45° angle that was kept constant. The sample volume had an axial length of 10 mm, and the depth was kept at 50 mm. A reference gate was placed in the damping layers at a depth of 35 mm. Two hundred plastic microspheres with a diameter of 80 μm and 200 gas bubbles with diameters from 8 to 25 μm were introduced into the system 20

cm upstream of the point of insonation. The gas bubbles were generated by electrolysis. The time when each plastic sphere or air bubble was introduced into the system was noted.

Three hundred artifacts were studied with an iridium background and 300 were studied with a pig blood background: 200 tapping the probe, 200 tapping the probe wire, and 200 tapping the silicone tube of the closed-loop system. This gave a total of 600 artifacts.

In Vivo Studies

Patients

Automatic transcranial embolus monitoring was carried out for 1 hour on the right MCA in 15 patients with a mechanical heart valve. None of the heart valve patients had previous symptoms suggesting cerebrovascular disease, and none had evidence of atherosclerosis on color duplex examination of the major precerebral and intracranial arteries.

Embolus monitoring was also carried out on the ipsilateral MCA of 45 patients with internal carotid artery stenosis that reduced the diameter by ≥70% on color duplex examination. Of these patients 39 were symptomatic and 6 were asymptomatic. This gave a total of 60 hours with online automatic transcranial Doppler cerebral micro-embolus monitoring.

In 5 of the mechanical heart valve patients and 5 of the carotid stenosis patients, the following artifacts were also assessed during monitoring: 10 moving the skin near the probe, 10 tapping the probe, 10 tapping the skull, 10 clenching the teeth, 10 swallowing, 10 talking (counting), 10 wrinkling the forehead, and 10 coughing. This gave a total of 800 artifacts.

Data Analysis

The in vitro and in vivo Doppler studies were automatically assessed online by the instrumentation and stored on the instrument's hard disk. The threshold for high-energy signal detection in this study was 20 dB · ms as described earlier. Detection of a high-energy signal was automatically followed by a decision as to whether it was an embolus or artifact. The hard-disk data were also assessed offline by an experienced observer blinded to the automatic assessment using standard criteria for embolus detection.¹⁹ The times of each embolus detected by the instrumentation were compared with those noted by the experienced observer. The artifacts were made by the experienced observer and automatically assessed by the instrumentation online. Emboli identified only by the instrumentation and not noted by the observer were assessed as if the observer had considered them artifacts. The observer's assessment was used as the gold standard, and the sensitivity, specificity, and κ values for multifrequency Doppler were calculated according to standard statistical practice.²⁰

Results

In Vitro Studies

All 200 single plastic spheres and all 200 microbubbles were automatically detected and correctly classified online. All 600 artifacts in the in vitro studies caused a Doppler energy increase of >20 dB · ms and were therefore detected by the instrumentation. Five hundred ninety-six (99.3%) were correctly classified as artifacts, whereas 4 (0.7%) were classified incorrectly as emboli. Therefore, multifrequency TCD had an in vitro sensitivity for embolus detection of 100% and a specificity of 99.3% (κ=0.992, P<0.001).

In Vivo Studies

Mechanical Heart Valve Patients

The EmboDop automatically detected 525 emboli during the 15 hours of online monitoring in the 15 mechanical heart valve patients. The experienced observer detected 521 em-

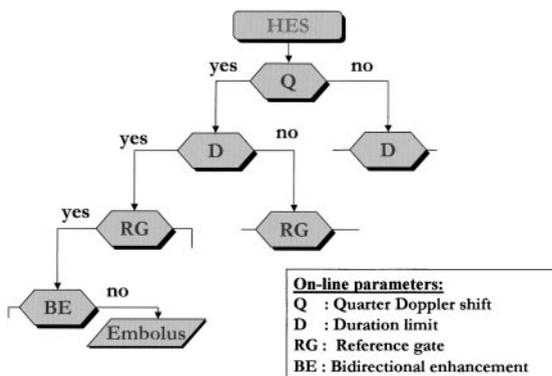


Figure 5. Four parameters are used in an optimized binary decision tree for automatic differentiation between emboli and artifacts. HES indicates high-energy signal.

boli. There was agreement between the EmboDop and observer assessments for 514 emboli.

Further analysis of the results showed that the 7 emboli detected by the observer and not by the instrumentation had been assessed as being due to artifacts. The 11 emboli detected by the multifrequency TCD and not by the observer were reviewed again by the observer, who thought that he had probably assessed 6 of them as normal-intensity variations and 5 as low-intensity artifacts in his blinded assessment.

Carotid Stenosis Patients

During the 45 hours of monitoring in the 45 carotid stenosis patients, the multifrequency TCD detected 35 emboli that exceeded the 20-dB · ms energy detection limit. All detected emboli occurred in 17 of the 45 patients (38%), and all were in patients who had previously been symptomatic. The experienced observer detected 33 emboli in his offline assessment. There was agreement between the automatic assessment and the observer for 32 emboli. Further analysis of the results showed that the embolus detected by the observer and not by multifrequency TCD had been assessed as an artifact. The 3 emboli detected by the instrumentation and not by the observer were reviewed again by the observer, who thought that he had probably assessed 2 of them as normal-intensity variations and 1 as a low-intensity artifact in his blinded online assessment.

Artifact Provocation

All 800 provoked artifacts in patients exceeded the detection limit of 20 dB · ms. Seven hundred ninety-one (98.9%) were assessed as artifacts; 9 (1.1%) were assessed incorrectly as emboli. The 9 artifacts assessed as being emboli by multifrequency TCD consisted of 4 skin movements near the probe, 3 wrinkling of the forehead, and 2 clenching of the teeth.

For the total 554 emboli and 800 artifacts detected by the experienced observer in the total patient population, the multifrequency Doppler had a sensitivity of 98.6%, a specificity of 97.2%, and a κ value of 0.953 ($P < 0.0001$).

Discussion

We have assessed the first multifrequency TCD system specially designed for cerebral embolus detection and found that it can automatically detect cerebral microemboli online with a high degree of sensitivity and specificity.

The first decision necessary for automatic embolus detection is to determine whether an increase in Doppler energy (ie, Doppler power increase times duration) is due to normal variations caused by Doppler speckle or the heart cycle or is due to an abnormal event, which may be either an embolus or artifact. This requires exact measurements of the relative Doppler power increase caused by an embolus compared with the normal background signal (embolus-to-blood ratio) with a high time resolution.

This is the first TCD instrumentation that carries out root-mean-square calculations of Doppler power with a time resolution of 2 ms. These power measurements are as sensitive as or more sensitive than 128 FFT with 6-kHz pulse repetition frequency, which is normally used. However, 128 FFT has a time resolution of 21.3 ms, which is much longer

than the 2 ms used by this TCD system. Although the time window with frequency analysis may be improved to 10.6 ms by using 64 FFT, this has the disadvantage of energy leakage caused by the FFT process, which results in underestimation of power measurements. The accuracy of measurements of a relative increase in Doppler energy depends on accurate measurements of the background power and the actual power increase caused by the event. This instrumentation uses a 30-ms period to measure the average background power. This period is long enough to take into account both the statistical variations in the Doppler signal resulting from speckle and the relative increase in power that occurs during systole compared with diastole because of the Windkessel effect. The high accuracy and reproducibility of the Doppler power measurements were confirmed in *in vitro* studies with plastic spheres of different diameters in which we found that power measurements with this system were in accordance with Rayleigh scattering²¹; ie, the amount of Doppler scattering was dependent on the sixth power of the plastic sphere diameter.

There remain several situations in which automatic embolus detection with multifrequency Doppler is difficult. We have found that automatic detection and counting are inaccurate when emboli pass through the sample volume very close together. This is the case in several clinical situations in which multiple gas bubbles may be introduced into the cerebral circulation. These include carotid and coronary intra-arterial angiography, carotid angioplasty and endarterectomy, left ventricular assist devices, and heart surgery. Another obvious situation occurs when multiple contrast bubbles are introduced into the cerebral circulation. However, single bubbles will be identified and counted if they do not pass through the sample volume at exactly the same time. Another problem is overloading of the instrumentation. Experience from *in vitro* studies suggests that this may be the case when gas emboli $>40 \mu\text{m}$ or solid emboli $>450 \mu\text{m}$ pass through the sample volume. This problem will be reduced in the near future by addition of an automatic gain to the instrumentation. Finally, very small emboli (gas <2 to $3 \mu\text{m}$ or solid $<80 \mu\text{m}$) may cause such a small increase in Doppler energy that they do not exceed the detection threshold of the instrumentation. Event-related data, all the raw data, or both may be stored on the hard disk, which allows offline analysis of periods during monitoring when automatic detection is difficult. These data may be reassessed by an observer or by an offline method such as wavelet analysis.²²

The more accurate measurements of Doppler energy give increased sensitivity with regard to embolus detection and facilitate differentiation between small solid emboli and speckle. We have found that Doppler speckle may cause variations in Doppler energy of up to 12 dB · ms, eg, an embolus-to-blood ratio increase of 3 dB that lasts <4 ms when recording MCA flow velocities with a normal signal-to-noise ratio. Therefore, we have used in this study an abnormal increase in Doppler energy or high-energy signal as an increase in Doppler energy of >20 dB · ms (ie, an increase in Doppler power of at least 5 dB that lasts >4 ms). We have tested this energy detection limit during 5 hours of recording of the MCA in 5 healthy individuals in whom there was a normal signal-to-noise ratio in the Doppler spectra and found

no signals that exceeded this energy level. Different detection thresholds, however, may prove to be more appropriate in other clinical situations.

Lack of a clear definition of threshold levels may explain the large variations in the incidence and frequency of cerebral microemboli reported in similar patient groups.^{1,3,4,13,14} We therefore propose that the threshold level for microembolus detection in all future studies should be clearly defined as an energy threshold rather than a decibel limit. This definition should also include a clear description of how the background power level and embolus-to-blood ratio have been measured and the time resolution for the power measurements. In this study, we found on several occasions that the experienced observer did not recognize a Doppler energy increase of 20 dB · ms. This strongly suggests that the human ear is often not sensitive enough to accurately assess the Doppler energy increase caused by small solid microemboli, especially during long-term monitoring.

This new multifrequency Doppler system can differentiate between high-energy signals caused by emboli and those caused by artifacts with a relatively high degree of specificity. This has been obtained by characterization of the detected high-energy signals with several additional new parameters in a Boolean decision tree that was optimized by exposing it to many different types of embolic signals.

Emboli showed the quarter shift parameter because they moved through the sample volume and were insonated simultaneously with both 2.0 and 2.5 MHz. This parameter is in accordance with the Doppler principle itself and has not been used previously because this is the first available multifrequency TCD system.

The very high time resolution of the system enables very exact measurements of the duration of the high-energy signals. This can then be compared with the calculated maximum duration limit that it cannot exceed if an embolus is the cause of the energy increase.

Multigate Doppler with 2 sample volumes placed a distance from each other has previously been assessed for differentiating between emboli and artifacts.¹⁷ This was accomplished by measuring the time taken by the embolus to travel from the first to the second gate. However, it is often difficult for the examiner to place both sample volumes in the vessel with a long enough distance between them, and the results may be very difficult to interpret.^{23,24} We used a second sample volume as a reference gate.¹⁷ This sample volume is placed a longer distance from the first and not necessarily in the vessel under study. This is practically much easier for the examiner. The results are also easier to interpret because an artifact will produce a high-energy signal in both sample volumes simultaneously or with a time difference of <4 ms. If an embolus should also cause an energy increase in the reference gate because of side slope effects, the anatomy of the vessel, or the teardrop shape of the sample volume, then there will be a time delay of ≥ 4 ms.

The last parameter is bidirectional enhancement in both positive and negative velocities. This well-known characteristic of artifacts is due to fast vibrations of the transducer or tissue in both directions.

The combination of all 4 parameters in an optimized binary decision tree resulted in accurate decisions as to whether increases in Doppler energy were due to emboli or artifacts.

Several methods have previously been assessed for automatic embolus detection. Neural network had a relatively good specificity but did not achieve a sensitivity high enough for routine use.²⁵ In addition, this method cannot be used online because of the considerable computer capacity required. Wavelet analysis and matching pursuit^{26–28} have shown considerable promise offline, but the computer needs for data analysis also exclude them at the moment from online clinical use.

Keunen et al²⁹ reported promising preliminary results using nonlinear forecasting in the time domain to differentiate embolic signals from Doppler speckle and artifacts. Later, Cullinane et al³⁰ assessed this algorithm in the frequency domain using filtered FFT data. They found good sensitivity and specificity when they assessed the algorithm with previously recorded tape data containing emboli from patients with carotid stenosis and after carotid endarterectomy. This study also demonstrated considerable differences in sensitivity and specificity when 2 hours of tape data were assessed by 6 additional expert centers. This underlines the need for Doppler instrumentation that clearly defines its threshold limit in the detection of abnormal Doppler energy increases that may be due to emboli. Disagreement between human experts may be explained at least in part by desynchronization when the same tapes are replayed through different Doppler instruments. We have found that embolus-to-blood ratio measurements may differ by as much as 2 dB when nonsynchronized tapes are played through a number of Doppler instrumentations from the same manufacturer.

In conclusion, this is the first study in which online automatic cerebral embolus detection with multifrequency TCD has been assessed. We found that multifrequency Doppler can automatically detect cerebral microemboli with a relatively high sensitivity and specificity. Our hope is that this method will help to improve standards for the sensitivity and specificity of cerebral microembolus detection and improve the unacceptable differences in observer assessments that have accompanied this method for the past 10 years.

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