Can Transcranial Doppler Discriminate Between Solid and Gaseous Microemboli?
Assessment of a Dual-Frequency Transducer System

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Background and Purpose—Transcranial Doppler ultrasound can reliably detect both gaseous and solid cerebral emboli. However, conventional equipment is unable to discriminate between gaseous and solid emboli. This is a major limitation in situations in which the 2 coexist, because they may have very different clinical relevance. Recently, a novel Embo-Dop system, using insonation at 2 ultrasound transducer frequencies, has been developed. An initial study with a small sample size suggested it provided excellent discrimination. We performed a validation study in subjects with embolic signals of known nature.

Methods—Gaseous embolic signals were obtained in 7 patients with known patent foramen ovale by intravenous injection of agitated saline injections. Solid embolic signals were obtained in patients with symptomatic carotid stenosis (N = 23). Discrimination of the 2 using the Embo-Dop system dual-frequency system was assessed. It was compared with discrimination using embolic signal maximum intensity with an intensity threshold.

Results—One hundred forty-five solid embolic signals were recorded from carotid stenosis patients. Seventy-three were classified as solid and 72 as gaseous by the Embo-Dop system. Six hundred forty-eight gaseous embolic signals were recorded from 7 patients with patent foramen ovale. Six hundred twenty-five were classified as gaseous and 23 as solid. This gave a sensitivity of 50.3% and specificity of 96.5% for detecting solid embolic signals. Discrimination was better than using a simple intensity threshold.

Conclusions—The Embo-Dop dual-frequency system allows better discrimination than a simple intensity threshold but it is not accurate enough for use in clinical or research studies. Further work is needed to develop reliable clinical systems for discrimination of emboli. (Stroke. 2005;36:1731-1734.)

Key Words: cerebral circulation ■ embolism ■ ultrasonography, Doppler, transcranial

Embolism is the most common mechanism causing stroke and is also an important cause of neurological complications occurring during operations and interventional procedures. Transcranial Doppler ultrasound (TCD) can detect both gaseous and solid asymptomatic emboli. The detection of gaseous emboli was first described in the 1960s in decompression sickness1 and during cardiopulmonary bypass surgery.2 In the latter, the number of embolic signals (ES) has been correlated with cognitive outcome2 and has been shown to be reduced by various operative procedures.4 The detection of solid emboli was first described in the 1990s.5 Presumed solid ES have been found in patients with a wide variety of potential embolic sources. Most work has been performed in symptomatic carotid arteries stenosis, in which the presence of ES predicts further stroke and transient ischemic attack risk.6–9 The technique is widely used for monitoring during carotid endarterectomy, and asymptomatic ES during both the dissection and postoperative phase have been shown to correlate with peri-operative stroke and transient ischemic attack risk.10,11

A major problem, particularly when recording during operative interventions, is the failure of conventional TCD equipment to differentiate between solid and gaseous emboli. This is important because the neurological consequences of a few larger solid emboli are likely to be much greater than those from many hundreds of tiny microbubbles. This has severely limited the use of the technique in situations in which both gaseous and solid emboli can occur, such as between arterial opening and closure during carotid endarterectomy. Early studies demonstrated that the mean intensity increase with gaseous emboli was higher than that with solid emboli including platelet aggregates and thrombi.12–16 However, signal intensity also increases with embolus size, and if neither size nor composition is known accurate classification is impossible. Furthermore, although using intensity increase alone allowed gaseous emboli to be discriminated off-line with a specificity and specificity of ≈90%,16 this is insufficient for clinical practice. During many situations when gaseous emboli occur, many hundreds or thousands may be

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produced; therefore, unless the specificity is near 100%, a significant number will be misclassified as more clinically significant solid emboli.

Recently a new method using a dual-frequency transducer has been developed commercially.\textsuperscript{17} The first results were published in this journal and suggested a high sensitivity and specificity in discrimination between gaseous and solid emboli. This work built on previous theoretical and experimental work, suggesting that the relative intensity of gaseous to solid ES differed when insonated by different emitting ultrasound frequencies.\textsuperscript{18} The novel system uses a dual frequency transducer emitting 2 frequencies (2.0 MHz and 2.5 MHz) and compares the relative intensities of the signal at both frequencies. However, the validation analysis was on relatively few embolic signals in patients, including only 32 ES caused by presumed solid emboli.\textsuperscript{17} There have been no published replication studies. Therefore, we assessed this commercially available system in groups of patients in situations in which it was known whether the ES were caused by solid or gaseous emboli. ES resulting from gaseous emboli were obtained by agitated saline injection in patients with known patent foramen ovale (PFO). ES caused by solid emboli were obtained from monitoring in patients with symptomatic carotid stenosis.

Subjects and Methods

Consecutive patients with symptomatic carotid stenosis (>50%) were identified from an acute stroke and transient ischemic attack service. Patients with PFO, confirmed on transesophageal echocardiogram, and with no other potential cerebral embolic source, were recruited from the same stroke service and also cardiology outpatient clinics. The local hospital ethics committee approved the protocol, and all patients signed informed consent.

Equipment

The recently developed Embo-Dop Transcranial Doppler System (DWL Ltd) system was used (Multi X-laboratory, version 2.1, English). This insonates simultaneously at both 2.0 and 2.5 MHz. We used standard system settings designed to optimize ES detection as recommended in Consensus criteria.\textsuperscript{16} Mean depth was 50.4 mm (SD 3.8). A sample volume of 5 mm was used, although in a few cases this had to be increased to obtain an adequate signal. Power was 64 to 100 mW. Recordings were performed from the ipsilateral middle cerebral artery in carotid stenosis subjects. Bilateral middle cerebral artery recordings were performed in the PFO patients. The transducer was held in place by a proprietary headpiece supplied with the system.

In patients with carotid stenosis, recording was performed for 1 hour. In patients with PFO, recordings were performed for 2 minutes after injection of an agitated air and saline solution; 9 mL of normal saline was mixed with 0.5 mL of air and 0.5 mL of the patient’s blood and agitated between 2 10-mL syringes through a 3-way tap, and 5 mL of this agitated bubble solution was then injected into the patient before each 2-minute recording. The intravenous cannula was flushed between injections to prevent possible injection of clotted blood from within the cannula.

The Embo-Dop system uses an event detector system using a previously published algorithm to identify potential candidate events.\textsuperscript{20} It then applies a second algorithm, using the data from the dual-frequency insonation, to determine whether each ES is gaseous or solid.\textsuperscript{17} We used this event detection system to identify ES. The spectra from all saved embolic signals were recorded onto the hard drive of the computer. All signals were reviewed by an observer experienced in ES detection. Using standard consensus criteria,\textsuperscript{19} true ES were identified. These ES were used for further statistical analysis.

Data Analysis

The system categorizes ES into solid ES and gaseous ES using a threshold based on the difference in embolic signal ratio (DEBR) of the intensities of the ES measured using the 2 transducer frequencies. The system categorizes ES into definite solid, possibly solid, definitely gaseous, and possible gaseous. An ES is reported as definite solid if the DEBR is between –0.62 and 1.82, possible solid if DEBR is between –0.82 and –0.62 or between 1.82 and 2.02, definite gaseous in DEBR is < –1.02 or > 2.22, and possible gaseous if DEBR is between –0.82 and –1.02 or between 2.02 and 2.0. We determined the sensitivity and specificity of the Embo-Dop system for discriminating between gaseous and solid ES, assuming that all ES in the carotid stenosis group were caused by solid emboli, and all ES in the PFO group were caused by gaseous emboli. We performed sensitivity and specificity for detecting both solid and gaseous emboli in 3 ways: (1) our primary prespecified analysis considered all ES categorized as definite or possible solid emboli by the software as solid emboli and all categorized as definite and possible gaseous emboli as gaseous emboli; (2) a secondary analysis considered only those ES categorized as definitely solid by the software as solid emboli, whereas those categorized as possible solid, possible gaseous, and definitely gaseous were considered as nonsolid emboli; (3) a secondary analysis included only ES with an intensity when insonated at 2 MHz of > 7 dB. This is because this threshold is frequently used in clinical and research studies using ES detection to improve specificity.\textsuperscript{7,19}

We compared the sensitivity and specificity ratios obtained using the dual-frequency approach, with that obtained using intensity alone to discriminate gaseous from solid emboli. For this analysis we used data from the 2-MHz transducer alone. Sensitivity and specificity were determined using decibel thresholds between 5 and 20 dB, with the intensity level measured using the automatic intensity algorithm on the Embo-Dop. To directly compare the specificity of both methods at the same sensitivity, values corresponding to the sensitivities obtained using the Embo-Dop method were obtained from the receiver operator curves for the intensity threshold method.

Results

Recordings were obtained from 23 symptomatic carotid stenosis patients and 7 patients with PFO. In the PFO patients, a total of 50 contrast injections were performed. A total of 793 ES were recorded. Of these, 648 were in PFO subjects and 145 were in carotid stenosis subjects.

Of the 145 ES in the carotid stenosis endarterectomy patients, 73 were classified as solid (65 definite and 8 possible) and 72 as gaseous (60 definite and 12 possible). Of the 648 ES in the PFO patients, 625 were classified as gaseous (624 definite and 1 possible) and 23 were classified as solid (20 definite and 3 possible).

Sensitivity and specificity for detecting solid and gaseous emboli are shown in the Table. In our primary analysis, in which both definite and possible solid ES were considered as solid emboli, this gave a sensitivity of 50.3% and specificity of 96.5% for detecting solid ES. The sensitivity and specificity values for solid and gaseous emboli are shown on a receiver operator curve in the Figure. On the same curve are plotted sensitivity and specificity values using an intensity threshold, with intensity measurements made from the 2-MHz recording to discriminate gaseous and solid emboli. These are plotted for 1-dB increments between 5 and 20 dB. It can be seen that the discrimination obtained with the Embo-Dop is slightly better than that obtained using a simple intensity threshold. In discrimination of solid emboli, for the same sensitivity of 50.3%, the specificity using the intensity threshold method was 94.2% compared with 96.5% for the Embo-Dop method. In discrimination of gaseous emboli,
for the same sensitivity of 96.5%, the specificity using the intensity threshold method was 25.7% compared with 50.3% with the Embo-Dop method.

Results of our secondary analyses are shown in the Table. When only ES categorized as definitely solid were categorized as solid, the sensitivity declined from 50.3% to 44.8%, but the specificity increased slightly from 96.5% to 96.9%; 124 of the 145 ES in the carotid stenosis group and of the 631 of the 648 ES in the PFO group had an intensity increase >7 dB. When only these ES were included in the analysis, the sensitivity and specificity for detecting solid emboli were similar at 48.4% and 97.9%, respectively.

Discussion
Our results provide the first extensive evaluation of the first commercially available system for discriminating between gaseous and solid ES. Although the sensitivity and specificity values were slightly better using the Embo-Dop than when using a simple intensity threshold, we were unable to confirm the high sensitivity and specificity reported in the initial evaluation study. The sensitivity and specificity are not sufficient for use in clinical situations in which there are likely to be large numbers of gaseous emboli, of limited clinical significance, and much smaller numbers of solid emboli of major potential clinical importance. This situation is illustrated in a situation such as cardiac surgery or during interventional neuroradiological procedures when numerous gaseous emboli, but many fewer solid emboli, are believed to occur. For example, one can consider a situation in which there are 1000 emboli, only 5% of which are solid, with the remainder being gaseous. Even with a specificity for solid emboli as high as 95%, 50 of the 1000 signals will be misclassified as false-positive solid emboli. Even if all the 50

A plot of sensitivity against specificity for discrimination of solid and gaseous emboli. For each of gaseous and solid emboli, a single value is shown for the dual-frequency transducer method. Also shown are sensitivity and specificity values using an intensity threshold to discriminate, with values shown for a range of different intensity thresholds from 5 to 20 dB.
solid emboli are correctly classified as solid, because of the 50 incorrectly classified signals, the positive predictive value is only 50/100 or 0.5. This is insufficient for routine clinical use.

A previous experimental evaluation suggested that the use of a dual-frequency transducer could allow improved discrimination between gaseous and solid emboli. However, whether this information could be used with conventional TCD systems has been a subject of some controversy. In particular, it has been suggested that distortion of the ultrasound beam as it passes through the skull may make calculations obtained in the in vitro situation not valid during patient recording. Our results suggest that the dual-frequency approach does allow improved discrimination over the use of a simple intensity threshold but the difference is not sufficient to provide clinically a clinically useful technique. Our results show a lower sensitivity and specificity than that found in the initial evaluation. The reasons for this are uncertain, although we studied a larger number of solid emboli and therefore our estimate is likely to be more reliable.

We also evaluated performance using 2 other methods of data analysis. The Embo Dop system categorizes ES as either definite or possible solid or gaseous emboli. Essentially, these analyses use 2 thresholds for discrimination. Our prespecified primary analysis considered ES categorized as both definite and possible solid as solid emboli. A secondary analysis, applying the higher threshold, and considering only ES categorized as definite solid as solid resulted in a reduction in sensitivity of solid emboli from 50% to 45%, with a very slight increase in specificity. We also analyzed data considering only ES with an intensity increase >7 dB. Interobserver reproducibility in detection of ES >7 dB is higher, and ES above this threshold have been shown to predict stroke. These results were not very different from the primary analysis. Neither of these secondary analyses improved performance sufficiently to make the system sufficiently sensitive and specific for clinical use.

A technique that allows the discrimination of gaseous and solid emboli would widen the scope of TCD emboli detection. However, further work is required to develop a reliable clinical system. It is possible that further refinement of the dual-frequency approach may improve discrimination. We did experiment by altering the thresholds used for discrimination of the 2 materials and were unable to significantly improve performance. Therefore, the method would be likely to require significant developments to make it clinically useful. It has also been suggested that the use of harmonics and subharmonics may allow discrimination. Harmonics, at multiples of the transducer frequency, and in particular subharmonics, at fractions of the transducer frequency only occur with gaseous emboli. However, until such systems are developed into validated online systems, TCD can only reliably detect, but not discriminate between, gaseous and solid emboli.

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References


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