Online Automatic Discrimination Between Solid and Gaseous Cerebral Microemboli With the First Multifrequency Transcranial Doppler

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Background and Purpose—The aim of this study was to assess the first multifrequency transcranial Doppler system that was specially developed to automatically detect and discriminate between solid and gaseous cerebral microemboli.

Methods—The multifrequency transcranial Doppler instrumentation insonates simultaneously with 2.5 and 2.0 MHz. Differentiation between solid and gaseous microemboli is based on the principle that solid microemboli reflect more ultrasound at the higher than at the lower frequency, whereas the opposite is the case for gaseous microemboli. In the in vitro studies, 159 plastic spheres (50 or 80 μm in diameter) and 105 gas bubbles (8 to 25 μm) were studied in a pulsatile closed-loop system containing irodium or pig blood. 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—In the in vitro studies, 152 of the 159 (95.6%) plastic spheres were classified as solid, and 7 (4.4%) were classified as uncertain solid. Of the 105 gas bubbles, 99 (94.3%) were classified as gaseous and 6 (5.7%) as uncertain gaseous. Thus, correct classification was made for 251 (95.1%) of the 264 embolic events studied. A comparison between the automatic multifrequency discrimination and the known embolic classification gave a κ value of 0.897 (P<0.0001). The multifrequency Doppler classified 433 (84.2%) of the 514 emboli detected in the mechanical heart valve patients as gaseous, 74 (14.4%) as solid, and 7 (1.4%) as uncertain (3 uncertain solid, 4 uncertain gas). Thirty-two emboli were detected in 17 (38%) of the 45 carotid stenosis patients; 30 (93.7%) were classified as solid and 2 (6.3%) as uncertain solid.

Conclusions—This study has shown that multifrequency transcranial Doppler can be used to automatically differentiate between solid and gaseous microemboli online. Most detected microemboli in this initial study of mechanical heart valves were classified as gaseous, whereas most were classified as solid in the patients with carotid stenosis. (Stroke. 2002;33:1975-1980.)

Key Words: carotid stenosis ■ cerebral embolism ■ mechanical heart valve protheses ■ ultrasonography, Doppler
elements. Solid microemboli reflect more ultrasound power at a higher compared with a lower frequency, whereas the opposite is the case for gaseous microemboli. The aim of this study was to assess the first multifrequency TCD specifically developed to automatically detect and discriminate between solid and gaseous cerebral microemboli. Studies were first carried out in vitro and then in the clinical situation.

Materials and Methods

Doppler Instrumentation

The multifrequency Doppler instrumentation (EmboDop, DWL) insonates simultaneously with 2.0- and 2.5-MHz frequencies. The broadband dual-frequency probe specially developed for this system allows insonation with a special but similar spatial intensity distribution using the 2 different transmitting frequencies. The probe may be used at a depth between 45 and 80 mm, which is covered by the longitudinally stretched focus area of the ultrasound beam. This results in minimal difference in ultrasound beam distortion caused by the tissue layers and the temporal bone and prevents inaccuracies in the simultaneous EBR measurements at 2 transmitting frequencies.

The frequency responses of the 2.5- and 2.0-MHz Doppler audio channels have been made as similar as possible (difference 0.1 dB) by use of special low-pass filters. The system has a 128 Fast Fourier Transform 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 for artifact rejection. Embolus monitoring with this system may be carried out bilaterally with 3 Doppler channels on each side. Data can be continuously stored digitally on the computer hard disk for up to 4 hours with the possibility of transfer to an archive system.

The multifrequency TCD classifies microemboli depending on the difference between the EBR at 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation (dEBR). Upper and lower classification limits were determined before this study by in vitro testing with plastic microspheres and gas bubbles. The lower dEBR limit for discrimination was set at 0.83 ± 0.2 dB to take into account small variations in the background Doppler signal and in measurements resulting from beam distortion. The lower limit for solid emboli was therefore 0.83 dB. However, if the dEBR was within 0.2 dB of this limit (ie, between 0.63 and 0.83 dB), it was classified as uncertain solid. Microemboli with dEBR values below the 0.83 dB limit were classified as gaseous; if they were within 0.2 dB of this limit (ie, between −0.83 and −1.03 dB), they were classified as uncertain gaseous. Classification limits were introduced in an attempt to limit the possibility of errors resulting from resonance effects of very small gas bubbles, which cause a power increase of <7 dB. The higher dEBR limit for the classification of solid microemboli was 2.05 ± 0.2 dB. This limit has a slight slope of y = 0.02x + 2.05 dB, where y = dEBR and x = 2.0-MHz EBR. dEBR values above this level were therefore classified as gaseous; if they were within 0.2 dB of this limit (ie, between 2.05 and 2.25 dB), they were classified as uncertain gaseous. Solid microemboli were classified when the dEBR was below this limit and as uncertain solid if they were within −0.2 dB of this limit (ie, between 2.05 and 1.85 dB). Solid decisions were also classified as uncertain when the EBR value for 2.0-MHz insonation frequency was between 5 and 7 dB. This was also done to take into account possible resonance effects from gas bubbles with diameters of approximately 2.5 to 2.7 μm that could give dEBR values similar to approximately 80- to 86-μm solid microemboli.

In Vitro Studies

In vitro studies were carried out with a pulsatile closed-loop system (Figure 1). The silicone tubing had a diameter of 3 mm and was immersed in a water tank in which the water 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 iodinium-302 Pearl Luster Pigment Powder (Merck Co) for approximately half of the studies and pig blood for the remainder. The tubing was insonated through Plexiglas damping layers at constant 45° angle. The sample volume had an axial length of 10 mm, and the depth was kept at 50 mm.

We studied 119 plastic spheres with a diameter of 80 μm and 40 with a diameter of 50 μm. In addition, 105 gas bubbles with a diameter from 8 to 25 μm were generated by electrolysis. The plastic spheres and gas bubbles were introduced 20 cm upstream of the point of insonation.

Clinical Studies

Automatic transcranial embolus monitoring was carried out for 1 hour on the right middle cerebral artery (MCA) in 15 patients with a mechanical heart valve (MHV). None of the MHV 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 in 45 patients with an 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 of online automatic TCD cerebral microembolus monitoring in patients. Some of the data from these studies were also used in a study to assess automatic embolus detection online with EmboDop.

Embolus Detection

The threshold level for embolus detection in this study was defined as a relative Doppler energy increase of ≥ 20 dB · ms for which the Doppler power increase (EBR) is at least 5 dB and lasts >4 ms above the average background energy. Short-term power measurements were carried out every 2 ms on the basis of digital root-mean-square calculations and used to calculate a moving average for 30 ms of the background Doppler signal, which was updated every 2 ms. A relative Doppler energy threshold of 20 dB · ms was chosen to exclude normal Doppler energy variations resulting from Doppler speckle (random clustering of red blood cells).

Emboli were differentiated from artifacts by use of 4 parameters in an optimized binary decision tree: quarter Doppler shift, maximum duration limit, reference gate, and bidirectional enhancement. The hard-disk data were also assessed by an experienced observer blinded to automatic assessment using standard observer criteria for embolus detection. The times for each embolus detection by the instrumentation were compared with those for the experienced observer, and only those emboli on which both the automatic assessment and the observer agreed were used for the discrimination assessment.
Data Assessment

The accuracy of multifrequency TCD in differentiating the known gaseous and solid microembolic signals in the in vitro studies was assessed with a standard $\kappa$ calculation.\textsuperscript{21} For assessments of the results, an automatic classification of uncertain solid was considered a gaseous decision and an uncertain gaseous classification as a solid decision.

Results

In Vitro Study

In the in vitro studies, 152 (95.6%) of the 159 plastic spheres were correctly classified as solid (Figures 2 and 3), and 7 (4.4%) were classified as uncertain solid. None were classified as certain gaseous. The dEBR was $0.74 \pm 0.63$ dB for the 80-$\mu$m plastic spheres and $0.63 \pm 0.56$ dB for the 50-$\mu$m plastic spheres.

Of the 105 gas bubbles, 99 (94.3%) were classified as gaseous (Figures 3 and 4), and 6 (5.7%) were classified as uncertain gaseous. None were classified as certain solid. The dEBR of the 105 gas microemboli had a dEBR of $-3.51 \pm 0.94$ dB. Four of the 6 uncertain classification decisions were made when the pig blood background signal was used and 2 with the irodinium background. Therefore, correct classification was made for 251 (95.1%) of the 264 embolic events (plastic spheres and gas bubbles) studied. A comparison between the automatic multifrequency discrimination and the known embolic classification gave $\kappa = 0.897$ ($P<0.0001$).

Clinical Studies

A total of 514 emboli were detected in the 15 MHV patients and 32 in 17 (38%) of the 45 carotid stenosis patients. In the MHV patients, multifrequency TCD classified 433 (84.2%) as gaseous (Figure 5) and 74 (14.4%) as solid (Figure 6). A total of 7 (1.4%) were not given a definite classification (3 uncertain solid, 4 uncertain gaseous).

In the carotid stenosis patients, 30 (93.7%) of the 32 emboli were classified as solid (Figure 7) and 2 (6.3%) as uncertain solid. None were classified as gaseous.

Discussion

This study has shown for the first time that multifrequency TCD can differentiate between solid and gaseous microemboli. This is possible because the reflection of ultrasound power is dependent not only on the size of the embolus but also on its composition and the insonating frequency.

Figure 2. Plastic microsphere (80 $\mu$m) in the pulsatile closed-loop system with pig blood background. Reflected ultrasound at 2.5-MHz insonation (blue) is 0.6 dB greater compared with 2.0-MHz insonation (red).

Figure 3. In vitro study showing differentiation between 58 gas bubbles (8 to 25 $\mu$m) below the $-0.83 \pm 0.2$-dB dEBR lower limit and 58 plastic spheres (80 $\mu$m) between the lower $-0.83 \pm 0.2$-dB and upper 2.05 $\pm 0.2$-dB dEBR differentiation limits. Arrow, microsphere from Figure 2.

Figure 4. Gas bubble in the pulsatile closed-loop system with pig blood background. Reflected ultrasound is 4.8 dB lower at 2.5 MHz (blue) compared with 2.0 MHz (red).

Figure 5. MCA microembolus in an MHV patient that was classified as gaseous. Reflection is greater (13.9 dB) at 2 MHz (red) compared with 8.3 dB at 2.5 MHz (blue).
used.\textsuperscript{14,15} This is the case for microemboli with a diameter <300 μm for which the principle of Raleigh scattering applies\textsuperscript{22} and the insonation frequency is higher than the resonance frequencies of the emboli.

The upper size limit for detection is otherwise dependent on the absence of overloading, which most often is due to larger gas emboli. This problem can be overcome in the near future by installation of an automatic gain in this Doppler instrumentation. The lower diameter limit for embolus detection is determined by the background signal and therefore by the diameter of the insonated artery and the axial sample volume. An assumed axial sample volume of 10 mm, a mean MCA diameter of 3 mm, and a hematocrit of 45% would give an approximate theoretical lower detection limit for gaseous microemboli of 2 to 3 μm and a lower limit for solid microemboli of 80 μm.\textsuperscript{14,15} Previous clinical experience with TCD-detected asymptomatic cerebral microemboli suggests that their size normally is within these limits.

Individual detection and differentiation will be difficult when many cerebral microemboli pass through the sample volume at the same time. This may be the case when multiple gaseous emboli are introduced into the cerebral circulation, eg, during invasive diagnostic or therapeutic cardiovascular examinations and heart surgery. Studies of ultrasound contrast agents have also shown that resonance effects cause errors when monitoring very small gas bubbles that have a diameter of <3 μm (ie, a Doppler power increase of <7 dB). Classification limits (see Materials and Methods) for solid microemboli have therefore been introduced in an attempt to reduce this potential problem. However, a higher Doppler energy threshold of >28 dB·ms (Doppler power ≥7 dB times duration >4 ms) is more reliable for differentiation in clinical situations when very small microbubbles may be present.

There have been few reports to date on the problem of embolus differentiation. Devuyst et al\textsuperscript{23} recently reported that wavelet representation combined with dual-gate TCD had only fair accuracy in differentiating between solid and gaseous emboli. Wavelet analysis cannot at the moment be used online because of the considerable computer capacity required for data analysis.

A definite decision was made in this study for 94% of the emboli detected in the carotid stenosis patients, and all were classified as solid. In the remaining 6%, the decision was uncertain solid. None of the emboli in this patient group were classified as gaseous. These findings support the view that clinically silent cerebral microemboli in patients with carotid stenosis are predominantly solid in composition. Preliminary clinical studies have suggested that their frequency may be of prognostic significance\textsuperscript{24} and may be reduced by antiplatelet treatment.\textsuperscript{25} The most likely cause of solid microemboli in these patients would seem to be platelet aggregates or whole-blood clots formed at the site of the stenosis.

In the MHV patients, a definite decision was made for 98.6% of the 514 microemboli. Most (84.2%) were classified as gaseous, whereas 14.4% were solid and 1.4% were uncertain. The cause and clinical significance of gaseous and solid microemboli in MHV patients are uncertain. Indirect evidence suggesting that most are due to gas bubbles has previously been obtained through the use of oxygen inhalation, which reduced the number of microemboli by >50%, whereas their number increased under hyperbaric conditions.\textsuperscript{26,27} Cavitation just behind the valve leaflets may be at least partly responsible for gas bubble formation. However, cavitation bubbles do not normally last >1 ms, which is not long enough to reach the cerebral circulation.\textsuperscript{28} A possibility is that they become stabilized in some way, eg, by being coated with membrane fragments from platelets or other cells.\textsuperscript{29}

Solid microemboli in MHV patients may be due to activation of platelets or plasma coagulation on foreign surfaces, incomplete “washout” of blood from valves, and increased shear rates with secondary platelet activation.\textsuperscript{30,31} Air-fluid interfaces also activate platelets, which may be another mechanism generating platelet aggregation.\textsuperscript{31,32} No relationship has been found between the degree of anticoagulation assessed on a single international normalized ratio measurement and the total frequency of microemboli in MHV patients.\textsuperscript{4,5} In a retrospective study, an increased number of microemboli signals, platelet microparticles, and procoagulation activity were found in those patients who had experienced cerebrovascular symptoms, whereas there was no difference with regard to thrombin or fibrin generation.\textsuperscript{29} Although the addition of aspirin to anticoagulation therapy...
may reduce the risk of systemic embolism, it has not been shown to cause a significant reduction in the total frequency of microemboli.

Prospective follow-up studies are required to determine whether the relative frequency of solid and gaseous microemboli is a marker for increased stroke risk that could be used clinically to decide an optimal anticoagulation and antplatelet treatment or whether it may provide information on the relative merits of different valve designs. This would represent an important advance in patient management because the incidence of thromboembolic events in MHV patients is in the range of 1% to 5% per year despite oral anticoagulation. In most cases (~85%), the cerebral circulation is involved.

In industrialized countries, the replacement rate for heart valves is between 8 and 20 per 100 000. Because the risk is continuous and cumulative, thousands of strokes occur every year in this patient population, and ~5% to 10% of them are fatal.

We hope that the ability to automatically detect and differentiate between gaseous and solid cerebral microemboli will lead to a better understanding of the cause of cerebral injury in several other clinical situations. Cerebral microemboli are frequent during cerebral and coronary intra-arterial angiographies. They often occur during flushing and contrast injection when it is assumed that gas bubbles may also be injected into the cerebral circulation. However, they may also be due to loosening of atheromatous material from the arterial wall or thrombus formation on the tip of the catheter. Although the risk of neurological complications associated with intra-arterial angiography is uncommon, with a range of 0.55% to 3.2%, there is evidence to suggest that asymptomatic cerebral lesions may be relatively common. A necropsy study reported embolism after angiography that was thought to be catheter related in 30% of patients. Using diffusion MRI, Bendzus et al have recently shown signs of an embolic pattern of ischemic lesions in the distal vascular territory of small cortical, subcortical, or perforating vessels. They carried out 100 intra-arterial angiographies of the cerebral vessels and found 42 new MRI bright lesions in 23 patients.

Although mortality and morbidity are low during cardio-pulmonary bypass operations, postoperative cognitive impairment has been reported in relatively large numbers of patients. The incidence of cognitive decline has been reported to be at its highest (50% to 80%) at discharge, 20% to 50% at 6 weeks, and 10% to 30% at 6 months. A late decline to >40% predicted by the presence of early postoperative decline has also been reported after 5 years.

Cerebral microemboli have been implicated in the pathogenesis of this cognitive decline, and some studies have found a positive association between the number of intraoperative cerebral microemboli detected by TCD and postoperative neuropsychological outcome.

Differentiation between solid and gaseous asymptomatic cerebral microemboli would at least theoretically provide some information regarding embolus size. Microemboli that cause relative increases in Doppler power of 14 dB in the MCA are not uncommon in several clinical situations such as MHV patients. Theoretical calculations using an assumed MCA diameter of 3 mm and an axial sample volume of 10 mm suggest that this Doppler power increase may be due to a gas bubble that is 4 μm in diameter or a solid microembolus of 130 μm. This allows some assessment of the possible harmful effects because a 4-μm gas bubble should normally pass through the microcirculation (7 to 10 μm), whereas it may seem more difficult for a 130-μm solid microembolus. It is therefore a possibility that “asymptomatic” solid microemboli of this size may cause a progressive cognitive decline if they continuously enter the brain in large numbers.

In conclusion, this study has shown that it is possible to differentiate between solid and gaseous cerebral microemboli with multifrequency TCD. This new method may lead to new insights into the pathophysiology and prevention of stroke and may be of help in preventing cerebral injury during invasive cardiovascular examinations and surgery.

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