Detection and Volume Estimation of Embolic Air in the Middle Cerebral Artery Using Transcranial Doppler Sonography

Leonid Bunegin, BS; Denise Wahl, BS; Maurice S. Albin, MD

Background and Purpose Cerebral embolism has been implicated in the development of cognitive and neurological deficits following bypass surgery. This study proposes methodology for estimating cerebral air embolus volume using transcranial Doppler sonography.

Methods Transcranial Doppler audio signals of air bubbles in the middle cerebral artery obtained from in vivo experiments were subjected to a fast-Fourier transform analysis. Audio segments when no air was present as well as artifact resulting from electrocautery and sensor movement were also subjected to fast-Fourier transform analysis. Spectra were compared, and frequency and power differences were noted and used for development of audio band-pass filters for isolation of frequencies associated with air emboli. In a bench model of the middle cerebral artery circulation, repetitive injections of various air volumes between 0.5 and 500 μL were made. Transcranial Doppler audio output was band-pass filtered, acquired digitally, and subjected to a fast-Fourier transform power spectrum analysis and power spectrum integration. A linear least-squares correlation was performed on the data.

Results Fast-Fourier transform analysis of audio segments indicated that frequencies between 250 and 500 Hz are consistently dominant in the spectrum when air emboli are present. Background frequencies appear to be below 240 Hz, and artifact resulting from sensor movement and electrocautery appears to be below 300 Hz. Data from the middle cerebral artery model filtered through a 307- to 450-Hz band-pass filter yielded a linear relation between emboli volume and the integrated value of the power spectrum near 40 μL. Detection of emboli less than 0.5 μL was inconsistent, and embolus volumes greater than 40 μL were indistinguishable from one another.

Conclusions The preliminary technique described in this study may represent a starting point from which automated detection and volume estimation of cerebral emboli might be approached. (Stroke. 1994;25:593-600.)

Key Words • cerebral arteries • embolism • ultrasonics

Psychological and neurological sequelae following cardiopulmonary bypass have been the subject of recent clinical interest. Post-coronary bypass cognitive and neurological deficits have been related to several intraoperative conditions, among which are age, duration of bypass, and inadequate cerebral perfusion. Advances in Doppler sonography have enabled clinical investigations to monitor intracerebral hemodynamics during coronary bypass and to generate evidence that implicates embolic phenomena in the development of postoperative neuropsychological deficits. Much of the work correlating embolic incidents and psychological deficits relates patient neuropsychological status to total number of emboli detected in the middle cerebral artery (MCA) without consideration for type and volume. Discrimination between gaseous and particulate emboli, however, has been less concrete. Albin et al reported successful discrimination between gaseous and particulate emboli in a primate animal model based on peak Doppler shifts and maximal amplitude of the reflected signal. Qualitative differences in the geometric shape and gray scale intensity (signal amplitude) in the video image of the Doppler shift were identified. Distinct qualitative differences in the audio output that resulted from gaseous and particulate emboli were also described. Spencer et al, on the other hand, concluded that the transcranial Doppler (TCD) spectrograms recorded during their study did not exhibit sufficient differences between air bubbles and formed element emboli to warrant a claim of embolic differentiation. More recently, Markus and Brown and Russell et al demonstrated a limited ability to differentiate between the various types of emboli based on the intensity of the reflected signal. They were also able to quantify embolic volumes based on amplitude and signal duration measures. Unfortunately, the particulate types they studied all gave similar signal amplitude and duration profiles such that mixtures of the embolic types could not be resolved.

Using the criterion described by Albin et al for detection and identification of air emboli, Mitzel et al reported that alterations in the 6-week postoperative neuropsychological status of coronary artery bypass graft patients could not be statistically correlated to incidences of air embolism. This may be due in part to a threshold relation between these two measures, in that the brain may be able to tolerate small amounts of air, declining in function only after the entrainment of a threshold volume. As such, an estimate of embolic volume may be more useful than incidence data in developing a cause and effect relation between neuropsychological deficits and cerebral air embolism.

Based on the hypotheses that (1) the distinctive audible qualities that are heard when gaseous emboli
pass through insonated cerebral vessels can be used to identify air emboli and (2) the total power of those frequencies is proportional to the volume of the microbubbles, this study examined the characteristics of the TCD audio output during air embolic episodes and attempted to develop an analytic approach that would permit the isolation and volume estimation of embolic air. Initial experiments were carried out in an in vivo primate model. Additional experiments were performed on a biomechanical simulation of the MCA.

Materials and Methods

The underlying assumption on which this method is based requires that microbubbles pass through the Doppler field once and do not become entrapped within vortices or turbulent flow patterns within the insonated vessels.

In Vivo Experiments

Experiments were performed under a protocol approved by the Institutional Animal Care Committee. Macaque monkeys (weight, 5 to 8 kg) were anesthetized with 10 mg/kg of intravenously administered pentobarbital, intubated, and ventilated to maintain normal PaO₂ and PaCO₂. The left common carotid artery was dissected to the bifurcation of the internal carotid artery. The common carotid was ligated rostral to the bifurcation of the left common carotid artery was dissected to the bifurcation of the internal carotid artery. The common carotid was ligated rostral to the bifurcation and then cannulated caudal to the bifurcation in the cephalad direction with a 20-gauge angiocatheter, followed by attachment of a rubber injection port to the hub. Air was injected through this port with a precision Hamilton syringe having a 25-gauge needle. The needle was inserted so that it passed through the lumen of the angiocatheter until its tip protruded into the lumen of the common carotid artery.

A Medasonics Transpect Transcranial Doppler using a 2-MHz pulsed-wave Doppler probe was positioned over the left temporal window for insonation of the MCA. Five injections each of 0.5, 1.0, and 5.0 μL of air were made with a 5.0-μL syringe, and 10.0, 20.0, and 40.0 μL of air were injected with a 50-μL syringe. Injection time calibration was carried out by injecting the respective volumes of air (n=7) into fluid-filled tubing connected to a pressure transducer. Transducer output was directed to an oscillograph and the injection time taken as time required for the resulting pressure pulse to reach its peak. Injection times for 0.5, 1.0, and 5.0 μL were 0.044±0.03, 0.12±0.03, and 0.12±0.03 seconds, respectively. For the 10-, 20-, and 40-μL infusions, injection times were 0.07±0.01, 0.07±0.01, and 0.11±0.02 seconds, respectively.

Audio output from the TCD was recorded on cassette tape for later audio frequency analysis. Background audio was also obtained during periods that were confirmed to be clear blood velocity signals. Additionally, audio signals resulting from artifact were recorded by jarring the sensor and using an electrocautery to cut and coagulate tissue in close proximity to the Doppler probe. Signals were analyzed by fast-Fourier transformation (FFT) analysis using the FFT and spectrum modules in a LABWINDOS 1.2 environment. The air, background, and artifact FFT spectra were then compared by overlaying the respective spectra and visually identifying those frequencies that were principally associated with air and minimally associated with background and artifact. Those frequencies were then used for defining specifications for construction of an audio band-pass filter for Doppler signal conditioning.

In Vitro Experiments

A bench model of the MCA was devised comprising a segment of 3-mm (outer diameter) thin-walled silicone tubing imbedded in a thermoset polyvinylchloride (M-F Manufacturing Co) that was modified to have mechanical properties similar to those of brain tissue. The material was prepared by combining 1 part softener and 23 parts liquid polyvinylchloride (M-F Manufacturing Co) that was modified to have mechanical properties similar to those of brain tissue. The material was prepared by combining 1 part softener and 23 parts liquid polyvinylchloride and heating to 200°C followed by cooling to room temperature. This process yielded a material with a measured elasticity parameter G₀ of 40 mm Hg/mm. This value was similar to the G₀ measured in vivo in dogs by Walsh and Schettini. A rigid plastic shell 2 mm thick surrounded the preparation. A Medasonics Transpect 2-MHz pulsed-wave Doppler probe was positioned on the model so as to insonate the simulated MCA at an angle no greater than 10° from the vessel axis (Fig 1). A pneumatically controlled pump circulated simulated blood solution through the model. The simulated blood consisted of a mock serum prepared by mixing 87.8% normal saline and
12.2% pure glycerine, yielding a solution with a density of 1.0373 g/mL and a kinematic viscosity of 1.429 cp mL/g. This compared reasonably well with actual serum, which has a density of 1.0333 g/mL and a kinematic viscosity of 1.339 cp mL/g. To the mock serum, approximately 1 g/L of 5- to 10-μm-diameter polysulphone microspheres was added to mimic blood cells. Circulation parameters were adjusted to provide a flow pattern similar to that found in the MCA (systolic blood flow velocity of 70 cm/s and a diastolic velocity of 25 cm/s). Air was injected into the circulation model via a side port with precision Hamilton syringes such that all the air passed through the Doppler field. Audio output from the TCD was continuously recorded on cassette tape. Audio signals for air, background, and artifact were later analyzed by FFT. Comparisons were made by overlaying the respective spectra and identifying those frequencies that were principally associated with air. These harmonics were used for defining signal-conditioning parameters so that the frequencies associated with air could be isolated. FFT spectra were also compared with the corresponding spectra from the in vivo experiments. Volume calibration consisted of five injections each at 0.5, 0.75, 1.0, 2.0, 5.0, 10.0, 20.0, and 50.0 μL, using a Hamilton spring-loaded chromatography syringe (model CR-700-50). The 100.0-, 250.0-, and 500.0-μL volume injections were repeated five times by hand using a precision 500-μL Hamilton syringe. Injection time calibration was carried out as previously described. Injection times for the chromatography syringe were identical for each repetition and were 0.01 seconds for 0.5 μL, 0.015 seconds for 0.75 to 5.0 μL, and 0.02 seconds for 10 to 50 μL. Injection times for 100, 250, and 500 μL of air were 0.093±0.02, 0.14±0.01, and 0.22±0.03 seconds, respectively.

Transcranial Doppler audio output was continuously recorded on cassette tape for later analysis. Data tapes were played back, and the audio signal was conditioned, digitally acquired by a 386DX, 25-MHz microcomputer, then subjected to a Fourier frequency power analysis. The resultant frequency power spectrum was integrated to determine the area under the spectrum envelope and then related to the injected volume of air using a least-squares regression.

Results

The Fourier frequency analysis of the TCD audio segments obtained from the primate model contained...
frequencies between 100 and 500 Hz. The amplitudes of frequencies between 250 and 500 Hz were consistently and substantially greater than background when air emboli were present in the MCA. Dominant background frequencies appeared to be below 240 Hz, and the principal frequencies associated with artifact resulting from sensor movement and electrocautery were below 300 Hz and 125 Hz, respectively. Additionally, frequency power analysis on both background and artifact signals indicated that their dominant frequencies were on the order of ten times less in amplitude than the principal frequencies associated with air while minimizing the contribution of artifact and background primary harmonics. An acquisition trigger level of 0.75 V further minimized the influence of background and artifact.

Microbubbles with a volume of 0.5 \( \mu \text{L} \) were detected in three of five injections (60% of the time) in the in vitro model. At 0.75-\( \mu \text{L} \) volumes, detection increased to four of five injections (80%). For microbubble volumes between 1.0 and 40 \( \mu \text{L} \), detection was 100%, or five of five injections (Table). Integration of the conditioned audio spectrum represented total relative power and was linearly correlated to the injected air volume \( r^2 = 0.946 \) (Fig 3).

The TCD velocity waveform obtained from the bench model was similar to the waveform that was obtained from in vivo laboratory experiments (Fig 4a and 4c). Episodes of air embolism in the model produced the same characteristic hollow metallic auditory “chirp” and a high-velocity, short-duration spike on the video that was seen in the in vivo laboratory experiments (Fig 4b and 4d). The FFT spectra for air, background, and artifact were remarkably similar to those observed in vivo. The major background components were below 240 Hz, with artifact from sensor movement and electrocautery falling below 300 Hz and 125 Hz, respectively. As in the in vivo model, frequencies between 100 and 500 Hz were observed in the FFT spectra from the in vitro bench model. The harmonics between 250 Hz and 500 Hz were also substantially greater than background when microbubbles of air were present in the insonated vessel simulation. Audio outputs of the controlled volume injections were passed through the same eight-pole, 307- to 450-Hz band-pass filter and processed in a manner identical to that in the in vivo experiments. At 0.5-\( \mu \text{L} \) air volumes, emboli were detected in four of five injections (80% of the time). At volumes equal to or greater than 0.75 \( \mu \text{L} \), embolism detection increased to five of five injections (100%) (Table). Fig 5 shows the TCD video images of air emboli ranging in volume from 0.5 to 20 \( \mu \text{L} \). The relation between the injected microbubble volume and the total relative power of the respective audio spectrum appeared to take the form of a negative exponential (Fig 6). Regression modeling of the data to a negative exponential resulted in a significant correlation with an \( r^2 \) value of -0.86. The relation, however, showed linearity to the breakpoint at approximately 30 to 40 \( \mu \text{L} \) \( r^2 = 0.946 \). An order of magnitude difference in the regression coefficients (calibration line slope) between the in vivo and in vitro calibration curves was also noted (Fig 3).

Discussion

The extremely high ultrasonic reflectivity of gaseous microbubbles renders detection of gaseous emboli within the cerebral circulation using pulsed-wave TCD a relatively simple process. Hills and Grulke\(^{27} \) demonstrated that single bubbles as small as 0.03 \( \mu \text{L} \) could be detected with Doppler ultrasound and also described the effect of bubble velocity on the detection limit. In an in vitro model, Sellman et al\(^{28} \) described the detection of microbubbles on the order of 0.5 nL. The smallest microbubble (0.5 \( \mu \text{L} \)) that was detected by Albin et al\(^{29} \) produced a very high amplitude spike with a peak Doppler shift of at least 3000 Hz, while particulates (latex microspheres) produced spikes of significantly smaller amplitude with Doppler shifts that did not exceed 2400 Hz.

Fast-Fourier transform analysis of the TCD audio segments obtained from the in vivo primate model indicated that the principal frequencies that consistently appeared in the spectrum when air emboli were present in the MCA were between 250 and 500 Hz. These findings were somewhat surprising in that the identifying Doppler shifts for air were expected to be in excess of 2500 Hz. While these frequencies were present and measurable, the amplitude of the lower harmonics (250 to 500 Hz) was several orders of magnitude greater and more consistent than the parent frequencies.

However, the quantitation of microbubble volumes is somewhat more complex than simple detection and
requires that the gaseous microemboli pass through the insonated portion of the cerebral vessel one time without entrapment in turbulent flow patterns or vortices. Otherwise, the resultant Doppler signal will rise from more than a single interaction with the same microbubble, producing an overestimation of the volume measurement. Flow through the MCA is laminar (Reynolds number less than 100) for all but the most extraordinary conditions. The microemboli are also small enough to offer little resistance and thus are swept through the MCA at velocities comparable to that of the blood.

The first hypothesis imposes the constraint that the Doppler beam reflected from gaseous microemboli contains frequencies that can be used to unambiguously identify air emboli. The dominant frequencies specific to artifact generated by sensor movement and electrocautery appear to be lower and their power attenuated by an order of magnitude lower than frequencies associated with gaseous microbubbles. While Albin et al. were able to recognize qualitative differences in both the video and audio Doppler signals between gaseous and particulate emboli in an in vivo primate model, Spencer et al. were unable to distinguish between the two in the clinical setting. This confusion is not surprising in that the resolution of the various commercially available TCD monitors may vary substantially and may not be any greater than that needed to provide a visual description of the blood flow velocity envelope in as close to real time as possible. To achieve this, data acquisition, frequency analysis, assignment of gray scale intensities to the frequencies, and finally modulation to video output signals must all occur in an extremely short time to achieve “real-time” display. Rates and duration of data acquisition must therefore be kept to a minimum, followed by an FFT spectral analysis using as few points as necessary for blood flow velocity envelope resolution (typically 32- to 64-point FFT). Sampling windows of 10 milliseconds are typical in pulsed Doppler equipment and can only provide a maximal resolution of 100 Hz, which may not be sufficient resolution for discrimination between air and particulates. Additionally, the observations of Spencer et al. were made in a clinical setting where absolute conformation of the nature of the detected emboli was not possible. The identification of those TCD images could, at best, be educated estimates. Because the audio signal represents the raw Doppler shift, it may contain the information necessary for discrimination between air and particulate emboli. Extracting that information, however, appears to require more robust signal analysis than can be managed on-line by currently used TCD equipment.

The characteristic hollow metallic auditory “chirp” that has become accepted by many TCD users as the definitive signature of air emboli appears to be the product of component frequencies that lie between 250 and 500 Hz. Latex microspheres between 1 and 25 μm in diameter produced a sound similar to a “crackle” during experiments in a primate model. Because the acoustic impedance and density of latex is similar to those of blood flow components, it is likely that Doppler signals both in terms of frequency shift and amplitude will be comparable to those of particulate emboli. Both background and artifact also produce dominant harmonics (125 and 300 Hz, respectively).
which appear to only minimally overlap those of gaseous microbubbles and are substantially lower in amplitude.

The second hypothesis that the intensity or amplitude of the Doppler signal reflecting from gaseous microbubbles is proportional to the microbubble size also appears to be confirmed. Several studies have described the relation between reflected ultrasonic energy and bubble size. \(^{21-24}\) Sellman et al.\(^{25}\) demonstrated a positive exponential association between bubble diameter and Doppler amplitude between 10 and 160 \(\mu\)m. Two recently published reports confirm a similar correlation for thrombus, platelet, atheroma, and fat emboli.\(^{21,22}\) J.R. Klepper and M.A. Moehring point out, however, that the ultrasonic beam returning from the highly reflective air-blood interface can quickly saturate the video amplifiers of the TCD monitor, resulting in a maximum-intensity rail-to-rail spike for all but the smallest gas bubbles (unpublished data, September 1992). The audio amplifiers in the TCD equipment used in this study do not appear to be limited to the same extent as the video amplifier circuits. While the video image of a 0.75-\(\mu\)L bubble produces a full-scale deflection of high intensity (Fig 5), the total power for audio frequencies between 307 and 450 Hz appears to increase linearly up to bubble volumes of approximately 40 \(\mu\)L in the in vivo experiments and 20 to 40 \(\mu\)L in the bench experiments. Bubble volumes greater than 50 \(\mu\)L could not be differentiated based on the total power of the signature frequencies between 307 and 450 Hz (Fig 6). This suggests that the audio amplifiers are being saturated by the signal rising from the larger bubbles.
Doppler velocity envelopes observed in the in vitro and in vivo experiments were similar in shape and frequency composition. The thin-walled silicone for MCA simulation combined with a flow capacitor provided the facility for fine tuning of the flow patterns in the in vitro model. Additionally, the simulated blood solution used in the bench evaluation appeared to reflect incident ultrasonic frequencies similar to those found in blood. In a previous study, Spencer et al demonstrated that there were no differences between a suspension of Sephadex microspheres and sheep’s blood when evaluating Doppler waveforms in vitro. Miles et al and Spencer et al also showed that flow and Doppler measurements of pulsatility index and resistance index in their in vitro models correlated well with in vivo measurements.

Even though these results appear encouraging, it should be remembered that they were obtained under highly controlled conditions. Great care was taken to ensure that all aspects of the audio signal manipulation (that is, volume settings on the TCD, record and playback amplification, and acquisition parameters) were consistent throughout the volume range studied. However, the effects of small changes in sensor position relative to the insonated vessel that could occur during the course of monitoring on the linearity and slope of the correlation have not been evaluated. Other potential sources of error have been identified by Butler. Detection errors from encapsulated or coalesced bubbles would tend to reduce the reflected signal. An encapsulating layer around the air bubble would absorb a portion of the signal energy, resulting in underestimation. Coalesced bubbles, accumulating as foam, will present a nonuniform surface, scattering the incident sound energy and possibly reflecting signals containing complex waveforms that could be difficult to interpret. It is certainly possible that some combination of these factors may have played a role in the 10-fold difference in slope between the in vivo and in vitro calibration curves. Additionally, accurate focusing of the Doppler beam may have been hampered by the small dimension of the primate cranium. If the MCA was in reality closer to the probe than the minimum possible beam focal length (2.5 cm), less energy would be reflected, resulting in lower total power values for the emboli. Other detection difficulties that Butler identified as significant using continuous-wave insonation could possibly be avoided with pulsed-wave equipment. The ability to set the focal depth permits adjustment for optimal response. Insonation at an angle of 0° to 20° from the vessel axis will usually result in the Doppler field encompassing the entire vessel cross-section, thereby allowing detection of larger and more buoyant bubbles. Axial insonation with pulsed-wave equipment may also minimize the effect of overlying bubbles.

A significant amount of work is still needed to further delineate this approach. Important evaluations include the following: the effect of bubble velocity, in terms of location in the cardiac cycle, on the accuracy of the volume estimate; recalibration using calibrated microbubbles such as those described by Hills and Butler; and evaluating the various detection errors described by Butler on the calibration accuracy. Nevertheless, we feel that the preliminary technique described in this study provides a promising starting point for developed of algorithms that would be suitable for automated embolic volume estimation.

References


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L Bunegin, D Wahl and M S Albin

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