Transcranial Doppler Detection of Circulating Cerebral Emboli
A Review
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Background: The identification of gaseous emboli using Doppler ultrasound was described as early as the 1960s. Recently it has been demonstrated that this method can also detect solid emboli such as thrombi and platelet aggregates. This may make this technology useful in a large number of patients with, or at risk of, embolic stroke.

Summary of Review: Emboli appear as short-duration, high-intensity signals in the Doppler spectrum. The intensity of the Doppler signal from an artery containing an embolus depends on the density difference between the embolic material and blood. This difference is greatest for gaseous emboli, which are therefore the most easy to detect. Gaseous emboli have been demonstrated during deep-sea diving, and their presence correlates with the occurrence of decompression sickness. Similar signals have been detected during cardiopulmonary bypass. A relation has been demonstrated between the number of emboli detected by transcranial Doppler and a decline in neuropsychological function after cardiopulmonary bypass. Solid emboli such as thrombi and platelet aggregates result in less intense signals than air emboli. Their detection, using Doppler ultrasound, has recently been described in patients with prosthetic heart valves, atrial fibrillation, and carotid artery disease. It may also help in the detection and localization of embolic sources in patients with stroke. Studies in in vitro and in vivo models demonstrate that this technique provides information on the size and type of emboli. Larger emboli produce signals of greater intensity and duration. Practical patient monitoring will require automatic emboli detectors incorporated into the Doppler machine; such programs are being developed.

Conclusions: Detection of solid emboli using Doppler techniques offers an exciting new diagnostic tool. It has been demonstrated that the technique can detect solid emboli. The prognostic significance of such emboli remains to be determined. It is hoped that the technique will allow detection of patients at high risk of embolic stroke in whom appropriate prophylactic treatment can then be instituted. (Stroke 1993;24:1246-1250)

Key Words • Doppler • embolism • ultrasonics

The first report of the detection of asymptomatic solid cerebral emboli in patients with cerebrovascular disease, using Doppler ultrasound, has been followed by great interest in the subject, with the first International Consensus Conference on Embolus Detection taking place in Winston-Salem, NC, in September 1992. Although this technique has been used to detect gaseous emboli for some time, the potential to detect solid emboli could result in it becoming applicable to the much larger number of patients with cerebrovascular disease. Potential major uses include the identification of patients at high risk of subsequent clinical embolic stroke and the determination of the presence and site of an embolic source in individual patients.

Theoretical Background
In 1842 Christian Doppler described the physical phenomenon that has been named the Doppler effect; it is the basis on which ultrasound is used to provide information on blood flow velocity. This effect relies on the shift in the observed frequency of a radiated wave motion when there is relative movement between the source of the radiation and the observer. Red blood cells act as a moving reflector, and from the frequency shift between the transmitted and received ultrasound the blood flow velocity can be calculated. This technology is now widely used in all branches of vascular medicine. For the calculation of flow velocity, the frequency of the returned ultrasound signal is analyzed, and no use is made of the intensity of the returned signal. However, this latter parameter provides information on the material that the ultrasound beam meets, and theoretically it could be used to detect circulating emboli.

The intensity of the returned ultrasound depends on the proportion of the transmitted beam that is reflected. This in turn is dependent on the type of tissue through which the ultrasound is passed. The proportion of ultrasound reflected at the interface between two materials, such as that between blood and an embolus, is proportional to the difference in acoustic impedances of the two materials. Acoustic impedance itself depends on density; therefore, the greater the difference in density
between the two media, the greater the amount of ultrasound reflected, and the greater the intensity of the received signal. For particles with a size equal to or smaller than the wavelength of the transmitted ultrasound (0.77 mm for a standard 2-MHz transcranial Doppler probe), the amount of ultrasound reflected is governed by Rayleigh scattering rather than by direct reflectance as described above. Here the particle scatters the received ultrasound in all directions, and that portion directed back to the reflecting probe is detected. However, the amount of scattering, and therefore the ultrasound reflected, is also dependent on the densities of the two media. Both of these mechanisms will therefore result in an increase in intensity occurring when an embolus passes through the ultrasound beam; this should theoretically allow the detection of circulating emboli in the bloodstream. The magnitude of this increase will depend on the difference in density (and therefore acoustic impedance) between the embolic material and blood.

**Gaseous Emboli**

Air has a very low density, resulting in a large difference between its acoustic impedance and that of blood. Therefore, gaseous emboli should be easy to detect, and indeed their detection was described as early as 1965. Doppler techniques to detect gaseous emboli have made major contributions in two main areas: decompression sickness and cardiopulmonary bypass.

**Decompression Sickness**

Rapid return to the surface from deep ocean dives results in a symptom complex commonly referred to as the “bends.” During any dive inert gas, mainly nitrogen or helium, undergoes passive solution in the body. On ascent the decompression results in this gas coming out of solution in an uncontrolled fashion, forming bubbles in the circulation and tissues. These can lead to small-vessel blockage and tissue damage. Ultrasonic emboli detection was applied to this field as early as the 1960s. Gillis et al. surgically implanted a Doppler ultrasonic blood flowmeter on the vena cava of a pig and demonstrated high-intensity signals, which they believed represented gaseous emboli, occurring during decompression. Such signals, identical to those produced by the introduction of air bubbles, are clearly audible as characteristic “chirping” sounds and are the result of the frequency components being centered on a narrow frequency band. Spencer and coworkers, placing implantable ultrasonic probes on the descending aorta and inferior vena cava in sheep, demonstrated that these gaseous emboli appeared in the vena cava at much lower pressures than were required to produce embolic signals in the carotid artery and that the lungs acted as an effective filter that prevented the passage of air from the venous to the arterial circulation. This particular observation is in accord with the recent demonstration of an association between a patent foramen ovale in divers and an increased risk of developing decompression sickness.

Initial human studies demonstrated similar gaseous emboli in divers in decompression chambers. Ultrasonic probes were placed over the precordial area and veins to monitor gaseous emboli occurring during decompression at different rates, and a relation was demonstrated between gaseous emboli and clinical bends. Six divers were also studied in both the laboratory decompression chamber and immediately after ocean dives. The two divers who developed numerous gaseous emboli in the decompression chamber also developed the most numerous emboli after open dives; both developed the bends. These data were then used to provide recommended decompression limits, and Doppler detection of gas bubbles continues to be used in this field.

**Cardiopulmonary Bypass**

Earlier retrospective studies of cardiopulmonary bypass found the incidence of postoperative neurological deficits to be as low as 3%. However, subsequent prospective studies with full neuropsychological assessment have revealed that, while focal deficits are indeed rare, significant cognitive impairment occurs in a third or more patients. As early as 1913, it was suggested that air embolism occurring during left-sided heart operations represented a potential hazard. It is only now, largely as a result of the use of Doppler emboli detection, that the true relation of air embolism to postoperative neuropsychological outcome is emerging.

In 1965 Doppler sonography was first used to detect air bubbles in the extracorporeal circuit in animals put on cardiopulmonary bypass. Bubbles were photographed passing through the sample volume, and high-intensity Doppler signals were noted concurrently. Shortly afterward, similar embolic signals were noted in patients during bypass both in the extracorporeal circuit and in human vessels. More recently, transcranial Doppler techniques have allowed insonation of the middle cerebral artery, and using a monitoring probe with a head fixation apparatus it is possible to record from the same position for prolonged periods of time. Using this technique, it has been demonstrated that cerebral air embolism occurs at the time of aortic cannulation, during initiation of bypass, and intermittently throughout bypass. These air bubbles are reduced by using a membrane rather than a bubble oxygenator and by using a filter in the arterial line. Whether this air embolism is clinically important remains uncertain; recently two prospective studies, each in more than 50 patients, have found a significant positive correlation between the number of embolic signals detected during cardiopulmonary bypass and an impairment in postoperative neuropsychological function.

**Solid Emboli**

The Need for a Test to Detect Circulating Emboli

Cerebral embolism is the underlying pathogenic mechanism in many cases of stroke. Earlier clinical studies estimated that approximately 15% of all ischemic strokes are cardioembolic; emboli may also arise from carotid lesions, aortic plaques, and intracranial atherosclerotic stenoses. Recent trials have clearly demonstrated that stroke risk in patients with embolic sources can be markedly reduced by appropriate prophylactic treatment, particularly warfarin in the case of atrial fibrillation and carotid endarterectomy in symptomatic carotid stenosis. Nevertheless, a considerable number of patients need to be treated to prevent each stroke; in the case of atrial fibrillation, one stroke...
is prevented for every 40 patient-years of treatment with warfarin. Assuming that asymptomatic emboli are predictive of an increased risk of subsequent clinical emboli, Doppler detection of asymptomatic cerebral emboli may allow identification of those at highest risk of stroke, enabling more specific targeting of treatment.

Current diagnosis of embolic stroke rests on an investigational approach of “guilt by association.” A lack of validated, reliable clinical diagnostic criteria for cardioembolic stroke hampers individual patient treatment and challenges the accuracy of prevalence estimates. The likelihood of identifying a potential cardioembolic source for brain ischemia clearly depends on how thoroughly patients are evaluated and what lesions are accepted as potentially cardioembolic. This may explain the widely differing prevalence of cardioembolic stroke in different studies. For example, in one large multicenter stroke data bank project a 19% prevalence of cardioembolic stroke was reported. However, within each of the four centers the prevalence varied from 13% to 34%. The situation is made even more complex by the coexistence of potential cardioembolic sources with cerebral atherosclerosis, which may also be responsible for the stroke. A review of cerebral arteriograms performed in 50 consecutive patients with transient ischemic attacks that had a potential cardioembolic source found additional significant ipsilateral carotid atherosclerosis in 19 (38%).

The ability to detect circulating cerebral emboli would clarify the clinical picture in such cases. In the presence of both a potential cardiac embolic source and a carotid stenosis, recording from vessels in both hemispheres would allow determination of which is the important embolic source by determining whether emboli are detected unilaterally on the side of the carotid stenosis or bilaterally. Simultaneous monitoring above and below a carotid stenosis would also provide useful localizing information.

Early Studies

In the 1970s Doppler techniques were used in subjects undergoing total hip replacement to detect abnormal signals in venous flow thought to represent fat emboli. However, this initial observation was not taken further, and the current interest in solid embolus detection follows the recent report of signals believed to represent solid emboli, in the middle cerebral artery, detected during carotid endarterectomy. Air emboli had been reported previously during carotid endarterectomy, particularly during shunting and after release of the cross-clamp, but Spencer and coworkers also noted signals of lesser intensity before opening of the artery. They concluded that these must represent solid emboli dislodged during dissection of the surrounding tissues. Since then a number of groups have reported similar signals in recordings from the middle cerebral artery in patients with carotid stenosis and valvular heart disease and from the common carotid artery of patients with atrial fibrillation and recent myocardial infarction. As yet, these results are only in abstract or case report form.

Detection of emboli in such situations may prove to have profound clinical significance; they may have a similar significance to transient ischemic attacks and allow selection of patients requiring further specific treatment, either medical or surgical. However, as with any new technique, a degree of skepticism is necessary, and validation studies are essential.

Do these high-intensity signals represent emboli, or could they be caused by artifact or unusual and turbulent flow patterns? Spencer et al reported the characteristic features of embolic signals to be transience (lasting 0.01 to 0.1 second), an audible chirping quality caused by their being centered on one frequency, and an intensity of up to 40 dB greater than that of the Doppler signal from blood alone. In a rabbit validation model, the distal aorta, which is approximately the same diameter as the human middle cerebral artery, was sonicated while emboli, with widths of between 0.4 and 1.5 mm, were introduced proximally. Short duration signals, with an intensity at least 15 dB greater than that from the surrounding blood, were seen on every occasion that thrombus, platelet, atheroma, and fat emboli were introduced. These findings have been replicated in a sheep model using a similar transcranial Doppler system to sonicate the distal carotid artery. Atheromatous platelet and thrombus emboli with a width as small as 0.24 mm were detected. Therefore, solid emboli can produce high-intensity signals, although the emboli in these models were much larger than those likely to be responsible for the asymptomatic Doppler embolic signals detected in humans. The question remains: Are all the signals detected in humans actually emboli? The main differential diagnosis is probe motion artifact, which may occur during any movement, including talking. Artifacts have been reported to be bidirectional, have a wider frequency spectrum, and display the highest energy in the lower frequencies. Although usually bidirectional, predominantly unidirectional artifact can be produced (H.M., unpublished data), and this may be difficult to differentiate from embolic signals occurring in the lower frequency range. In practice certain signals can be clearly detected as showing features typical of emboli, whereas for a few signals, predominantly those with lower velocities, differentiation between embolus and artifact remains difficult. For this reason, if the technique is to be validated it is essential that rigorously blinded studies be performed in which the Doppler signals from both normal subjects and patients are recorded and analyzed by an observer blinded to the clinical history.

Future Directions

What further refinements in the technique are likely? Two promising areas are the ability to characterize individual emboli and the development of automatic emboli detectors. It has been suggested that, by analysis of the Doppler signal, information about the nature and size of an embolus may be obtained. A relation between size of embolus and intensity of signal has been reported both in vivo and in vitro. Both studies have also demonstrated that different embolic materials result in different intensity signals. For example, a thrombus embolus produces a more intense signal than a similarly sized platelet embolus. However, using signal intensity alone it is currently impossible to determine whether a given signal is from, for example, a larger platelet aggregate or a smaller thrombus. Recently it has been reported that the duration of high-intensity signal is highly correlated with the embolus size, and this may offer possibilities in sizing emboli, although
further validation is required in vivo. Assuming that the ultrasonic scattering characteristics of the different pathological cerebral embolic materials change independently over a range of frequencies, the use of a combination of different carrier frequencies may allow further characterization of embolic materials. A variety of transducer frequencies have already been used in a small series of subjects with emboli resulting from prosthetic cardiac valves; lower frequencies resulted in the highest sensitivity for emboli detection.41

Visually analyzing individual recordings is a time-consuming process. The optimum duration of recording for emboli is uncertain but likely to be at least 30 minutes. In three patients with symptomatic carotid stenosis who demonstrated such embolic signals, only one embolus was noted every 38 minutes in the ipsilateral middle cerebral artery.33 If the technique is to become clinically useful, some form of automated detection system is required. An ideal detector should have a high sensitivity for embolic signals and be able to differentiate them from normal variations in intensity of signal caused by blood flow alone or from artifact such as probe motion. It should be able to detect and save any relevant segments of recording, which can be reviewed later. Early automatic detection devices noted a sudden increase in intensity of the returned signal42; however, this does not differentiate artifact from embolus. Pattern recognition systems appear to offer the most promising approach; recently a program has been developed that detects the typical unidirectional, frequency-focused increase in intensity occurring with an embolus; it is programmed to ignore signals having the spectral displays typical of artifact.43 Early validation studies suggest that it is both sensitive and specific for off-line analysis,44 and an on-line version is currently being evaluated.

Solid embolus detection offers an exciting new diagnostic tool. The technique needs to be refined further, particularly with the development of automatic counting systems, although adequate automated counting systems are likely to be commercially available before long. The important question that will take longer to answer is the prognostic significance of these embolic signals and whether they have a potential similar to that of transient ischemic attacks in the identification of patients at high stroke risk.

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