Monitoring Embolism in Real Time
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We have known since the 17th century that emboli can cause stroke but, despite their occasional visualisation in the retinal circulation, a diagnosis of embolic stroke is usually one of “guilt by association,” which is made by the detection of an appropriate embolic source in a patient with stroke. Frequently, >1 potential embolic source exists; determining which is clinically relevant may be impossible. The indirect diagnosis of embolic stroke also results in management difficulties in stroke prevention. For example, in atrial fibrillation, treatment failure can only be determined by the onset of stroke or systemic embolization. Recently, studies have evaluated a technique that allows the direct visualisation of circulating emboli. This offers exciting potential applications in both the diagnosis and management of patients at risk of cerebral and systemic embolism.

Since the 1960s, we have known that gaseous emboli can be detected in blood using Doppler ultrasound. The large acoustic impedance difference between air and blood results in a scattering of ultrasound at the blood-air interface and a marked increase in received ultrasound intensity as the bubble passes. This results in a brief, high-intensity signal. This technique was applied to develop safe decompression limits in divers and to investigate air embolism during cardiopulmonary bypass. In 1990, while recording for air emboli during carotid endarterectomy, similar signals, but of lower intensity, were noted during manipulation of the carotid bifurcation.1 This was before arterial opening and, therefore, these signals could not represent air emboli; it was suggested that they represented thrombus and platelet emboli. Despite initial scepticism that these signals represented anything other than artifacts or flow turbulence, it has been clearly demonstrated experimentally that thrombus, platelet, and atheroma emboli result in these characteristic Doppler signals.2

The technique is highly sensitive and specific, and similar signals cannot be produced by flow turbulence or artifacts.2 The lower limit of detection remains unknown; the smallest thrombus and atheroma emboli that could be introduced experimentally were 200 to 400 μm in diameter.2 Confirmation was obtained that such signals represented emboli in a patient in whom a shower of embolic signals (ES) was noted in the middle cerebral artery coincident with the onset of contralateral hemiparesis and ipsilateral retinal emboli.3 ES have been reported in patients with a wide variety of potential embolic sources, including carotid stenosis, atrial fibrillation, and cardiac valvular disease, but they have not been found, or are rare, in age-matched controls.4 They are also common during interventional procedures, including cerebral and coronary angiography, carotid angioplasty, carotid endarterectomy, and cardiopulmonary bypass.

ES appear as short-duration, unidirectional, high-intensity signals within the flow spectrum on the fast Fourier transform spectral display. The intensity increase is frequency-focused (ie, maximal over a narrow frequency range), and signals are accompanied by a characteristic chirping sound. In contrast, the intensity increase due to an artifact is bidirectional and maximal at low frequencies. This difference usually allows easy differentiation of ES from artifacts,5 except on rare occasions in which a predominantly unidirectional intensity increase occurs that is maximal at low frequency; the use of a multigate transducer allows unambiguous differentiation.5 Interobserver reproducibility studies have demonstrated excellent agreement between experienced observers in identifying ES above a certain intensity threshold, but less good agreement for very low intensity signals.6 This has led to the suggestion that an intensity threshold should be used as an additional criteria for ES detection.5 Technical aspects of both signal acquisition and processing can influence ES detection; recommended international standards have recently been published.5

This technique offers a unique window to study the pathogenesis of embolism in humans. One striking feature is the high frequency of asymptomatic ES in patients with potential embolic sources. During a single hour of recording, ES can be detected in 30% to 40% of patients with recently symptomatic carotid stenosis and in 4% to 20% of patients with asymptomatic stenosis.4 On reflection, this is perhaps less surprising in view of the frequency of finding small, clinically asymptomatic emboli at postmortem in the carotid arterial territory of patients who die of stroke.7 Embolism is, therefore, a dynamic process with a number of factors determining the clinical consequences of a single embolus. These include the characteristics of the embolus itself, the frequency of other emboli in the same vascular bed, and the nature of the recipient vascular bed, including collateral supply and perfusion pressure.

A recent published debate presented divergent views on the clinical utility of this technique.8 Part of this confusion arises from the failure to distinguish between the clinical relevance of ES in different pathological conditions (in particular, where ES are caused predominantly by gaseous bubbles, as in patients with prosthetic heart valves, and conditions where they result from solid emboli, such as carotid stenosis). The
utility of ES as a surrogate marker for clinical embolism risk clearly depends on the ability to predict the relevant clinical end point. Increasing evidence suggests that in certain conditions, ES do identify individuals at increased risk. The technique has been most evaluated in patients with carotid stenosis, in whom ES are more frequent in subgroups known to be at increased stroke risk. In 2 small, prospective studies in patients with symptomatic and asymptomatic carotid stenosis, the presence of ES independently predicted subsequent transient ischemic attack and stroke risk; a large multicenter study (the Asymptomatic Carotid Emboli Study) is trying to replicate these findings. The potential application of this technique in patients with carotid stenosis is clear. The Asymptomatic Carotid Atherosclerosis Study demonstrated that in asymptomatic carotid stenosis, 85 carotid endarterectomies need to be performed to prevent 1 stroke over a 1-year period. Stroke in these patients is believed to be usually embolic and, therefore, the detection of ES to identify a high-risk subgroup has obvious appeal.

Asymptomatic embolization has also been reported in patients with a variety of potential cardiac sources of embolism. Early reports noted a high frequency of ES in patients with mechanical prosthetic cardiac valves, compared with infrequent signals with porcine xenografts. However, in this patient group, no relationship was found between the ES and clinical evidence of embolism, degree of anticoagulation, or plasma concentrations of coagulation markers. ES in patients with mechanical valves are of greater intensity than those in carotid stenosis, which is consistent with most of them resulting from gaseous emboli that are possibly formed as cavitation bubbles. A gaseous nature is supported by a reduction in their frequency after the administration of 100% inspired oxygen. Perhaps surprisingly, in view of its importance on a population basis, few studies have been performed in patients with atrial fibrillation. The prevalence of ES in this group seems lower than that in patients with carotid stenosis, but further studies are required to evaluate the clinical relevance of these ES. ES have also been detected after myocardial infarction, distal to middle cerebral artery stenosis and carotid dissection, in antiphospholipid syndrome, and in peripheral arteries distal to iliac stenosis, iliac angioplasty, and aortic aneurysms.

An exciting application of this technique is in evaluating novel antiplatelet treatments. Currently, a large gulf exists between in vitro or ex vivo determination of therapeutic efficacy with platelet aggregation or activation studies and large, expensive clinical trials. Because of the much greater frequency of asymptomatic ES compared with stroke, their use as a surrogate end point may allow the determination of efficacy in small patient numbers. For any such model to have clinical relevance, it must have been shown that ES relate to outcome in that particular setting. This has been demonstrated after carotid endarterectomy. During the procedure, atheromatous plaque is removed, and the denuded area of endothelium is a potent stimulant for platelet adhesion. Asymptomatic embolization in the ipsilateral middle cerebral artery is frequent after the procedure, and high rates predict early postoperative stroke and risk of transient ischemic attack.

This model has recently been used to demonstrate the efficacy of S-nitrosoglutathione, a nitric oxide donor with proposed relative platelet specificity. A significant reduction in embolization in the S-nitrosoglutathione–treated group was achieved with a sample size of only 12 in each group, despite pretreatment of all patients with aspirin and intraoperative heparin. This model examines only one aspect of platelet pathophysiology, namely adhesion to an area of denuded endothelium. Applying the technique to other situations, such as angioplasty in a model of plaque rupture or a symptomatic carotid plaque, will allow the efficacy of novel agents to be determined in a comprehensive fashion. Such an approach may allow antiplatelet regimens to be optimized before the confirmation of efficacy in large clinical trials.

Technical advances will facilitate the transfer of the technique from the research laboratory to the clinical environment. These include automated signal analysis, the ability to differentiate between different pathological materials, and ambulatory ES monitoring. Currently, no reliable, commercially available, automated method of ES detection exists. The gold standard is to record the raw Doppler signal onto digital audio tape and subsequently play it back through the signal processor, reviewing it in real time both visually and audibly. This is time-consuming and not applicable in clinical practice. Simple, commercially available computer algorithms that detect any short-duration intensity increase across the entire frequency spectrum are not sensitive enough for routine use in patients with the less intense ES found in carotid stenosis. The major difficulty remains in the detection of low-intensity ES and in differentiation from Doppler speckle. Any method that increases the ES-to-blood signal-intensity ratio will improve detection. One such approach uses the fact that ES have an intensity increase that is maximal over a narrow frequency range. A frequency-filtering analysis approach increased ES relative intensity and, in an off-line system, detected ES in patients with carotid stenosis with a high sensitivity. This approach is being implemented on-line in a commercial system.

In certain situations, the ability to differentiate between solid and gaseous emboli may have clinical use. During interventional procedures such as angiography, carotid endarterectomy, and cardiopulmonary bypass, numerous gaseous emboli occur. In addition, fewer solid emboli probably arise, but these are likely to have greater clinical significance. For a given material, signal intensity rises with embolus size, but if neither material composition nor size are known, as usually occurs in clinical practice, accurate characterisation of individual emboli is impossible. There has been recent interest in the use of a dual-frequency transducer to differentiate between gaseous and solid emboli, relying on the observation that the relative ES intensity differs for different materials across frequencies. Insonation at 2 frequencies close to the 2 MHz frequency used for transcranial Doppler allowed for the differentiation between gaseous emboli and solid microspheres in vitro. The situation in vivo is more complex for a number of reasons, including beam irregularities resulting from nonuniform transmission of ultrasound through the skull. Further validation studies are required, both in vitro
using more clinically realistic embolic materials and with insonation through bone and in vivo.

Currently, recording times of 1 hour are recommended in nonoperative situations, such as carotid stenosis and atrial fibrillation. However, these provide only a brief window on what is a dynamic process. Repeating or prolonging recordings in patients with carotid stenosis increases the proportion of ES-positive patients, and the predictive value of the technique might be increased. New electronic and battery technology is allowing the design of portable transcranial Doppler systems, and once the problem of prolonged probe fixation has been overcome, these will allow ambulatory recordings to be made for 8 to 12 hours. The enormous amount of data resulting from such recordings will make automated analysis essential.

In conclusion, Doppler ultrasound offers a unique method for detecting emboli in real time and may have applications in risk stratification, in evaluating the effectiveness of novel therapies, and in perioperative monitoring. The clinical significance of ES will differ in different clinical situations and must be determined individually. Currently, Doppler ES detection remains primarily a research technique, but technological advances, particularly the development of effective automated detection systems, will allow its transfer to clinical practice.

References


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