Clinical Correlates of High-Intensity Transient Signals Detected on Transcranial Doppler Sonography in Patients With Cerebrovascular Disease

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Background and Purpose High-intensity transient signals detected by transcranial Doppler sonography have been associated with particulate cerebral emboli. Their clinical correlates are poorly understood. This study was undertaken to assess their relation to cerebral ischemia and to determine whether the severity of cerebral arterial stenosis has an impact on their occurrence.

Methods We studied 96 arteries in 75 consecutive patients with extracranial or intracranial arterial lesions or potential cardiac sources of cerebral embolism. Sixty patients had histories of cerebral or retinal transient ischemic attacks or infarcts, and 15 were asymptomatic. The diagnosis of ischemia was based on the clinical presentation and was supported by extensive laboratory testing. A transcranial Doppler sonography unit equipped with special software for emboli detection was used. Signals were selected based on criteria established a priori.

Results Signals were detected in the territories of 28.3% of symptomatic and 11.6% of asymptomatic arteries. The difference was significant (P=.045). When patients with suspected cardiac embolic sources were excluded, the difference between symptomatic (27.9%) and asymptomatic (2.9%) arteries remained significant (P=.003), and signals were more frequent distal to arteries with more than 50% area stenosis (23.5%) than arteries with stenoses equal to or less than 50% (3.7%) (P=.028). In patients with only extracranial internal carotid artery stenoses, the difference between these degrees of stenosis remained significant (P=.043).

Conclusions We conclude that high-intensity transient signals are significantly more common in the territories of symptomatic arteries and distal to lesions causing more than 50% stenosis. These findings may have diagnostic and therapeutic applications. (Stroke. 1994;25:1570-1573.)

Key Words • cerebral ischemia • cerebrovascular disorders • embolism • ultrasonics

Subjects and Methods

Patients The records of the Neurovascular Laboratory at the Boston Veterans Administration Medical Center were reviewed for consecutive patients who had received TCD embolus detection testing as part of their clinical evaluation between March 29, 1993, and February 11, 1994. The 83 patients who were thus identified had either been admitted to neurology or vascular surgery wards or were followed in the outpatient clinics with a diagnosis of cerebrovascular disease. Seven were excluded from further analysis because of a change in the original diagnosis of ischemic cerebrovascular disease after their evaluations were completed (n=2) or because their TCD or neuroimaging studies were considered technically unsatisfactory (n=5). An eighth was excluded because a diagnosis of idiopathic thrombocytopenic purpura was made in addition to that of transient ischemic attack (TIA). The remaining 75 patients consisted of 71 men and 4 women (mean age, 64.5 years [range, 28 to 82 years]). Sixty had histories of cerebral or retinal TIs or infarcts, and 15 were asymptomatic.

The diagnosis of TIA and cerebral infarction was based on each patient’s clinical presentation. It was supported by extensive laboratory investigations, including brain computed tomographic (n=44) or magnetic resonance imaging (n=44) studies. All patients were examined by one of us, and individuals with disorders that may mimic symptoms of cerebral ischemia, such as brain tumors, arteriovenous malformations, and subdural hematomas, were excluded, as were patients whose symptoms of cerebral ischemia could not be localized to a specific vascular territory. At the time of TCD testing, patients were receiving one or more of the following medications:
heparin (n=25), warfarin (n=14), aspirin (n=33), or ticlopidine (n=1). Nine patients were on no anticoagulant or antiplatelet treatment.

A total of 96 arteries, consisting of the supraclinoid internal carotid artery (ICA)/proximal middle cerebral artery (MCA) (n=94) or basilar artery (BA, n=2), were monitored for the presence of HITS in these 75 patients. TIAs or infarcts had occurred in the territories of 53 sonicated arteries (51 ICAs and 2 BAS), which are henceforth identified as "symptomatic" arteries. The remaining 43 arteries, all supraclinoid ICAs/proximal MCAs, are designated "asymptomatic" arteries. Twenty-two asymptomatic arteries were studied in 21 patients who had symptoms of TIA or cerebral infarction along the contralateral ICA or BA territories, and 21 were studied in 15 individuals with no previous histories of ischemic cerebrovascular disease. For symptomatic arteries, the interval between TCD testing and symptoms of cerebral ischemia was 12 days or less for 30 vessels and more than 12 days for 23.

Thirteen patients were considered to have a potential cardiac source of cerebral embolism: 6 were found to be in atrial fibrillation, 1 was transferred to the Stroke Service with an echocardiographically demonstrated left ventricular thrombus, and 6 had mitral or aortic prosthetic valves. Ten of these patients had histories of TIAs or cerebral infarctions. Since 18 arteries had been sonicated in these 13 patients, the remaining 78 studies were considered to represent "arterial" cases. Of the latter, 43 arteries were symptomatic and 35 were asymptomatic. It is recognized that the cardiac chambers may have been undiagnosed sources of emboli in some of the remaining 62 patients. Six of the 62 had intracranial stenoses located at the ICA siphon (n=3), MCA M1 segment (n=2, in 1 patient), and proximal BA (n=2), both of which were considered symptomatic. The remaining 56 patients had 71 cervical carotid lesions.

Cerebrovascular Imaging Studies

The severity of arterial stenosis was determined by cerebral angiography for 28 patients, color duplex imaging in 21, and magnetic resonance angiography in 13. These figures exclude the cardiac patients, some of whom also received cerebrovascular evaluation. With the exception of 2 patients whose radiology folders could not be located, all original films were reviewed. Official reports were used in those 2 cases to determine the degree of arterial stenosis.

Cerebral angiography consisted of either conventional or arterial digital subtraction techniques. The severity of arterial stenosis was measured by means of a formula modified from Wiebers et al16: % stenosis=(100[A-B]+100[A'-B'])/2, where A, A', B, and B' are measurements of visible lumen diameters on the x-ray film; A and A' are the residual lumen at its narrowest area of stenosis on anteroposterior and lateral views, respectively, and B and B' are the arterial diameters immediately beyond the lesion where the arterial walls are parallel on anteroposterior and lateral views, respectively.

Magnetic resonance imaging was performed on a 1.5-T General Electric Signa unit. Two- and three-dimensional time-of-flight angiographic images of the carotid bifurcations were obtained (system 5.2 platform). Each carotid bifurcation was projected at 30-degree increments covering a 180-degree rotation, and images corresponding to approximately the anteroposterior and lateral projections were selected to determine the severity of stenosis. The latter was determined by the method used for cerebral angiography and described in the preceding paragraph.

The duplex studies were performed on an Ultramark 9-HDI instrument (Advanced Technology Laboratories). The severity of stenosis was determined by a modification of the method of Bluth et al.17

TCD Studies

TCD studies were performed according to previously described methods.18 A TC-2000 instrument (Eden Medical Electronics/Nicolet) equipped with a 2-MHz probe was used for all studies. Embolus detection was performed as part of routine TCD testing with special software for emboli detection (5.3002 E BETA 08 and 5.40 E BETA 01 A). At the beginning of each study the probe was positioned against the temporal bone window and immobilized with the help of a specially designed head band. With the exception of 2 patients who were monitored for 25 minutes, the duration of each study was 30 minutes. The proximal MCA and supraclinoid ICA were sonicated at depths of sonication of 50 to 55 mm and 56 to 65 mm, respectively, and the BA was assessed at a depth of 100 to 110 mm. Emboli detection was initiated by switching to Embolus Program-RB6. Throughout each study an experienced technologist continuously monitored the instrument screen and the patient under study. The technologist was instructed to note all potential sources of artifact such as patient blinking and probe slipping and to save all signals that seemed visually 9 dB higher in intensity than the surrounding blood (color range of green to red) and that were associated with a chirping sound on the audio output. All signals were printed or saved on floppy disk at the end of the study for further retrospective analysis that was performed by measuring the duration and amplitude of each signal with the emboli detection programs. Accepted signals were unidirectional from the baseline and occurred randomly throughout the cardiac cycle. They lasted 25 to 100 milliseconds and had an intensity of at least 9 dB higher than that of surrounding blood (Figure).

Fifteen of the 75 patients had more than one emboli detection study, so that the total number of reviewed TCD studies was 97. In individuals with more than one TCD assessment, only the findings of the first study were included for data analysis.

Statistical Methods

Group comparisons were made with either the $x^2$ or Fisher's exact test (two-tailed). All statistical analyses were performed at the Data Coordinating Center of the Boston University School of Public Health.

Results

HITS were detected in 20 of 96 arteries (20.8%). Fifteen of 53 (28.3%) symptomatic arteries and 5 of 43 (11.6%) asymptomatic arteries had studies showing HITS. The difference between the two groups was significant ($P=.045$). When arteries from the 13 patients with cardiac embolic sources were excluded, the difference between symptomatic (12/43 [27.9%]) and asymp-
tomatic arteries (1/35 [2.9%]) remained significant (Р=.003). Further analysis excluding the 6 patients with intracranial stenoses again showed a significant difference between symptomatic (10/37 [27.0%]) and asymptomatic (1/34 [2.9%]) extracranial ICA stenoses (Р=.005).

The relation between severity of stenosis and presence of HITS was studied only in patients without cardiac source of emboli. Twelve of 31 arteries (23.5%) with more than 50% stenosis and 1 of 27 (3.7%) arteries with a severity of stenosis equal to or less than 50% had positive studies. The difference between the two groups was significant (Р=.028). When patients with intracranial lesions were excluded, HITS were detected in the territories of 10 of 44 (22.7%) ICAs with more than 50% extracranial stenosis and in 1 of 27 (3.7%) of those with lesser degrees of stenosis; the difference was significant (Р=.043).

Discussion

Our findings indicate that HITS detected by TCD in the distal ICA and proximal MCA or BA are significantly associated with cerebral ischemia in these arterial territories. In addition, we show that HITS are detected significantly more frequently distal to arterial lesions with more than 50% stenosis or occlusion than lesions causing 50% stenosis or less.

Cerebral ischemia is frequently attributed to emboli that originate in the cardiac chambers and at stenotic lesions along the aortic arch and cerebral arteries. The embolic theory is supported by postmortem, intraoperative, and angiographic studies showing emboli in cerebral arteries, by the observation of emboli in retinal arterioles during fundoscopic examination, and by laboratory models. The presence of TCD signals similar to the ones described in this report and distal to asymptomatic ICA stenoses, their absence distal to asymptomatic ICA lesions, and their response to anticoagulant treatment had already suggested a relation between these signals and cerebral ischemia. Our finding of a significant association between HITS and cerebral or retinal ischemia provides in vivo evidence supporting the notion of cerebral embolism and furthers the findings of previous TCD studies. It also suggests that monitoring for these signals may potentially have diagnostic and therapeutic implications. However, although a significant association is found in this study, a cause and effect relation remains to be demonstrated. In addition, because these studies were obtained after symptoms of cerebral ischemia were clinically evident, whether HITS are a risk factor for stroke is unknown.

The incidental finding of retinal emboli during routine fundoscopic examination indicates that not all emboli are associated with symptoms of ischemia. The finding of HITS in patients without new symptoms of cerebral ischemia subsequent to TCD testing confirms the notion of asymptomatic embolism and suggests that factors besides the mere presence of HITS may affect this association. Embolus size and composition, frequency of embolism, and condition of collateral flow to the hemisphere at risk are likely factors that determine the extent of cerebral ischemia. Because the characteristics of HITS, such as duration and intensity, correlate with the size and composition of corresponding particles, the preceding considerations suggest that some characteristics may be key determinants of the clinical significance of HITS. However, there is no consensus in the literature today regarding criteria for HITS selection. In addition, the detection of these signals is affected by TCD equipment settings at the time of insonation. Duration of transmitted pulse (sample volume) and programmed amplification (gain) are parameters that can affect an instrument’s sensitivity.

As a result, the sensitivity of instruments in detecting HITS can vary from one laboratory to another. The five criteria presented in “Subjects and Methods” were chosen arbitrarily. Although they are similar to criteria previously used by other investigators, they cannot be considered definitive. We suspect that the low frequency of HITS in the population we studied compared with the findings of Siebler et al and Grosset et al can be explained on this basis. The remarkable differences between the findings of these investigators also support our concerns regarding HITS selection criteria and equipment settings.

Although atheromatous plaques of the ICA origin causing only a mild degree of stenosis have been associated with symptoms of cerebral ischemia, there is a general consensus in the literature that severe stenoses are associated with a higher risk of distal cerebral infarction. Local turbulent flow can be detected by Doppler testing when the arterial area reduction reaches 50% to 60%, and distal hemodynamic impairment is usually associated with more than 70% reduction. Artery-to-artery emboli are thought to originate from these lesions and be carried downstream to occlude distal vessels. The association of HITS with arterial lesions causing more than 50% luminal stenosis confirms these considerations and suggests that not all cerebral arterial stenoses have the same potential for embolism. Such an effect, although suspected clinically, could not be previously demonstrated in vivo because of lack of a technology that permitted detection of emboli. Our finding also confirms and further extends the observations of other investigators. Patients studied by Diehl et al and Lash et al had similar signals in the territories of stenotic lesions. Siebler et al detected embolic signals distal to carotid lesions causing more than 70% stenosis, and Grosset et al have recently reported that embolic signals were present more frequently in patients with symptomatic large artery atherosclerosis than in individuals with lacunar infarcts. However, these reports did not specifically address the effect of stenosis severity on the occurrence of embolic signals.

Fifteen patients had more than one TCD study. To ensure uniformity, only each individual's first study results were used for the analyses presented in this study. HITS are detected at a higher frequency if testing is performed within 12 days from the onset of symptoms of cerebral ischemia. This variation in HITS detection frequency over time may have introduced an additional and unaccounted-for variable in our analyses. However, we suspect that this effect was minimal because 23 arteries were tested more than 12 days after the onset of symptoms of cerebral ischemia; had they been studied earlier, the frequency of symptomatic arteries with positive studies would have been higher, thus favoring our findings.
An important limitation of our study concerns the use of different technologies to measure the severity of arterial stenosis. This admittedly brings a degree of inconsistency to our methods. For that reason, we chose not to analyze our data using subgroups stratified according to small increments of severity of stenosis and opted to divide the study sample into only two subgroups based on the criterion of 50% arterial stenosis. When compared with cerebral contrast angiography, the accuracy of color Doppler sonography for diagnosing lesions causing less than 49% and more than 50% stenosis is in excess of 90%. The accuracy of two-dimensional time-of-flight magnetic resonance angiography is similar to that of color Doppler imaging. The high concordance between results obtained with the different techniques should minimize the error introduced by this methodological limitation. Despite these considerations, we recognize the need to complete a similar study using one technology, preferably cerebral angiography, to determine stenosis severity.

In summary, HITS can be detected distal to symptomatic arterial lesions causing more than 50% stenosis. Although technical difficulties concerning HITS acquisition and selection criteria remain unresolved, these findings may potentially have diagnostic and therapeutic applications.

References


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