CORRESPONDENCE

Cryptogenic Stroke

TO THE EDITOR: In the Clinical Practice article on cryptogenic stroke by Saver (May 26 issue),[1] the importance of transcranial Doppler ultrasonography was underappreciated. My colleagues and I,[2] as well as others,[3,4] have found that transcranial Doppler ultrasonographic studies with the use of agitated saline contrast material are more sensitive than transesophageal echocardiography (TEE) for the detection of patent foramen ovale.

Among 284 patients with an early right-to-left shunt (i.e., excluding pulmonary arteriovenous fistula), TEE missed 43 cases (15%) of patent foramen ovale. Among these 43 patients, 18 (42%) had high-grade shunts (Spencer Logarithmic Scale grade III to V, on a scale from 0 to V, with higher values indicating more embolic tracks),[2] which predicted the recurrence of stroke or transient ischemic attack better than either the presence of a shunt on TEE or the presence of atrial septal aneurysm or mobility.

The reasons that transcranial Doppler ultrasonography is more sensitive than TEE for detecting patent foramen ovale include the ability to perform a more vigorous Valsalva maneuver in the absence of sedation and the loud and obvious signal that is produced by bubbles on transcranial Doppler ultrasonography, which can be seen and heard in the online videos linked to our 2016 article.[2] Transcranial Doppler ultrasonographic studies with the use of agitated saline contrast material should be regarded as the first-line test in the diagnosis of patent foramen ovale,[5] not relegated to the status of a fallback for patients who cannot undergo TEE.

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Dr. Spence reports that Spencer Technologies recently gave his laboratory a 10% discount on the cost of repairs to its transcranial Doppler ultrasonographic equipment. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Saver advises testing for thrombophilia and screening for cancer in selected patients with cryptogenic stroke. Although inherited thrombophilia may be identified in patients with cryptogenic stroke, it is unclear whether a positive test leads to a change in treatment. A randomized trial of warfarin versus aspirin therapy in patients with ischemic stroke (26.1% of whom had cryptogenic stroke) showed no difference in the incidence of recurrent ischemic stroke or death (17.8% vs. 16.0%, P=0.25), including in the subgroup of patients with cryptogenic stroke (15.0% vs. 16.5%, P=0.68)[1] and in the subgroup of patients with patent foramen ovale (16.5% vs. 13.2%, P=0.49).[2] Whether the use of a direct oral anticoagulant offers benefits over aspirin is currently being tested in clinical trials (ClinicalTrials.gov numbers, NCT02239120, NCT02313909, and NCT02427126). The results of testing for thrombophilia also may not always determine the duration of anticoagulation.[3] Cancer screening with computed tomography (CT) or positron emission tomography–CT may not improve outcomes in patients, as shown by studies involving patients with venous thrombosis.[3] Thrombophilia or cancer may occasionally be associated with cryptogenic stroke. However, the routine use of expensive tests should be avoided unless test results alter treatment or improve outcomes.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Spence reviews important studies from his own group and others that show that transcranial Doppler ultrasonography can detect some cases of patent foramen ovale that are missed on TEE. However, TEE is preferred as a first diagnostic test not because it is more sensitive than transcranial Doppler ultrasonography for detecting patent foramen ovale but rather because it simultaneously screens for additional aortic and cardiac causes of ischemic stroke, including aortic-arch atherosclerosis and atrial appendage thrombi, that cannot be investigated by means of transcranial Doppler ultrasonography. When concern for patent foramen ovale is very high but TEE has failed to detect a right-to-left shunt, it is worthwhile to attempt shunt detection by means of transcranial Doppler ultrasonography.

Dhakal et al. note there is a paucity of data to determine the most cost-effective diagnostic workup for thrombophilia and occult cancer in patients with cryptogenic ischemic stroke. The lack of salient data is highlighted by the citations in their letter. With regard to testing for thrombophilia, they cite a trial that evaluated a potential treatment-effect modification by only a single hypercoagulable state and did so among patients with multiple ischemic-stroke subtypes, not just among those with cryptogenic ischemic stroke.[1,2] For occult cancer, they cite studies that involved patients with venous thrombosis, not those with cryptogenic ischemic stroke. The Clinical Practice article aimed to describe a selective, staged, and flexible workup that would be reasonable to pursue in patients with cryptogenic ischemic stroke, on the basis of currently available observational studies and randomized trials, pending the availability of additional data.

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Since publication of his article, the author reports no further potential conflict of interest.

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