The search for paroxysmal atrial fibrillation in cryptogenic stroke

Leave no stone unturned

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Atrial fibrillation (AF), a well-established cause of ischemic stroke, is found in up to 25% of first strokes.[1,2] Most patients with stroke from AF will benefit from anticoagulation for secondary stroke prevention, so finding AF as a cause of ischemic stroke is critical. Many patients with AF have paroxysmal AF (PAF), in which periods of normal sinus rhythm alternate with sometimes brief episodes of AF. Conventional monitoring for AF in the hospital or for a small number of days as an outpatient may therefore miss the diagnosis of PAF. Although most of the data to support anticoagulation for stroke patients with AF come from patients with continuous AF, PAF has a similar risk of stroke when compared to continuous AF[3,4] and there appears to be a similar benefit of anticoagulation in reducing the risk of stroke in patients with PAF.[3]

Up to 40% of ischemic strokes are categorized as cryptogenic because no cause is found after a thorough workup.[1] Many speculate that some patients in this category might actually have PAF that has escaped detection. To test the hypothesis that PAF might be underdetected during the hospital-based stroke workup, several groups have studied patients undergoing multiday outpatient monitoring studies to try to detect AF. For example, recent studies using surface EKG loop recorder devices in cryptogenic ischemic stroke patients for 21–30 days have found PAF in 12% (29/239, 95% confidence interval [CI] 8%–17%)[5] to 23% (13/56, 95% CI 13%–36%).[6]

In this issue of *Neurology*®, Cotter et al.[7] report on the use of a more invasive but potentially higher yield technology, an implantable loop recorder (ILR) with AF detection capability. ILR technology may have substantial advantages over previously developed methods for detecting PAF—the in vivo implantation improves recording quality, and the devices can record epochs of EKG data for up to 3 years. The major limitations of the technology include the surgical procedure required for device implantation, costs of implantation and monitoring, and the finite memory of the loop recorder that restricts full quantitative analysis of the duration of PAF epochs.

The Cotter et al. study found PAF in 25% (13/51, 95% CI 14%–40%).[7] PAF events lasted a median of 6 minutes and first events were detected as far out as 5 months from the start of recording (with several first events detected beyond 3 months). Discovery of PAF was associated with several other measured variables, including age, CHADS2 score, CHADS2-VASc score, interatrial block, frequency of atrial premature contractions, and indexed left atrial volume on echocardiography. The authors note that some or all of these factors might potentially be useful to "prescreen" patients to select high-risk patients for invasive monitoring.

These data underscore the importance of prolonged, high-quality recording to detect PAF. In a patient who requires 5 months of continuous recording to detect a first PAF event, no currently available noninvasive device would be able to make the diagnosis.

A study such as this raises a series of questions that represent the main source of debate in this field. When it comes to stroke risk, does the duration of individual PAF episodes matter, or is the driver of stroke risk the state of transition back and forth from an organized atrial contraction to a fibrillating atrium? If the duration of each episode does matter, how much total burden of PAF is required to raise a patient's risk of recurrent stroke above that of a stroke victim without any burden of PAF? Finally, there is the thorniest question of all: is there a crossover point at which a certain burden of PAF translates to a superiority of anticoagulation over antiplatelet therapy for secondary stroke prevention in these patients?

The answers to these questions will likely come in time, as more data from long-term monitoring of cryptogenic stroke patients are obtained. Luckily, Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF),[8] a controlled trial of 450 patients randomized to implanted monitors vs noninvasive monitoring, has completed enrollment, and results are expected in 2013. CRYSTAL-AF may serve as a validation of the Cotter et al. study, as it is using the same ILR device.

One approach would be to say that in patients with a history of stroke and no other discernable cause, "PAF is AF," and therefore anticoagulation should be strongly considered in these patients. In support of this position are post hoc analyses of large trials of anticoagulation in AF that included PAF patients—specifically Stroke

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Prevention in Atrial Fibrillation (SPAF) I–III[4] and Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W)[3]—which found similar stroke rates between continuous AF and PAF,[3,4] and a similar reduction in stroke rates with anticoagulation.[3] The more conservative approach would be to argue that PAF should not be conflated with continuous AF, and that a dedicated trial of anticoagulation vs antiplatelet therapy is required in a large group of patients who have had PAF detected by ILR after cryptogenic ischemic stroke.

Multiple observational studies have found similar results: noninvasive and minimally invasive monitoring techniques detect PAF in a substantial percentage of patients with cryptogenic stroke and most of the newly discovered PAF epochs last only minutes. Patients with a high burden of PAF will likely benefit from anticoagulation. In patients with a low burden of detected PAF, the decision of whether or not to anticoagulate remains a difficult one that should be approached cautiously. Further data are needed to address specifically the relationships among PAF burden, the risk of recurrent stroke, and the potential benefits of anticoagulation.

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