Catheter ablation has become an accepted treatment approach for drug-refractory, symptomatic atrial fibrillation (AF). The technical aspects of the procedure have evolved, but to a remarkable degree, the objective of the procedure is nearly the same as when it was first introduced: the electrical isolation of the principal trigger sites of AF, the pulmonary veins (PVI). The procedure has an excellent success rate and acceptable safety profile, although AF may not be permanently eliminated even if response is initially complete (1).

There are, however, a number of complications that are associated with the procedure. One of the rare but most dreaded complications of the procedure is systemic embolism, which typically presents as a transient ischemic attack (TIA) or stroke. The mechanism by which stroke occurs is likely thromboembolism in the majority of instances; however, embolism of air and/or coagulum likely contributes as well (2). To minimize embolic complications, most electrophysiology laboratories have developed standards for pre-, intra-, and post-procedural anticoagulation as well as management of intracardiac sheaths and catheters. Nonetheless, the most recent worldwide survey on catheter ablation of AF reported a 0.71% incidence of TIA and 0.23% incidence of stroke (3). To date, the incidence of thromboembolism has not been thought to vary with the energy source used for ablation.

As the technique for AF ablation has matured, new modalities of energy delivery are being introduced, primarily in an effort to make this complex procedure more efficient and accessible. Two of these new entries, cryoballoon and multielectrode phased radiofrequency (RF) pulmonary vein ablation catheter (PVAC), in comparison to the standard approach of RF delivery using an open irrigated tip catheter, are the focus of inquiry in the important study of Siklody et al. (4) published in this issue of the Journal. The data are derived from an observational series of 74 patients undergoing ablation at 3 centers in Europe; the study was stopped prematurely when an independent ethics committee noted a dramatically higher rate of silent brain infarction following ablation in the PVAC group.

The patients in this study were similar to many prior published series, although slightly older. More than 60% of the patients had paroxysmal AF, which is typical, and the remainder had persistent AF. All patients underwent PVI alone without any additional linear or nonlinear left atrial ablation. The groups were well matched. All patients had similar pre-, intra-, and post-procedural care, including anticoagulation, level and duration of energy delivery, and performance of transesophageal echocardiography (TEE) to exclude pre-existing thrombus. They did not undergo intracardiac echocardiography. The 27 patients who underwent irrigated RF ablation had lesions placed in a circumferential fashion around each ipsilateral pair of PVs. The 24 patients who underwent cryoballoon ablation had balloons sized according to TEE-measured diameters; touch-up using a focal cryoablation catheter was performed if isolation was not achieved with the balloon alone. The PVAC was used in 24 patients. It is a circular mapping and ablation system capable of duty-cycled phased unipolar and bipolar RF delivery at low energy levels to specific electrodes or pairs of electrodes, without internal or external irrigation. All patients, irrespective of technique, were required to achieve complete PVI, and indeed, all met this procedural endpoint. Ultimate clinical outcome, that is, AF suppression, was not reported.

What is reported is a marked disparity in incidence of new embolic events as detected by brain magnetic resonance imaging (MRI). All patients underwent a pre-ablation (1 day prior) and a post-ablation (within 2 days) scan. New embolic events were documented in 7.4% of irrigated RF patients, 4.3% of cryoballoon patients, and 37.5% of PVAC patients, statistically different among groups \((p = 0.003)\). The PVAC patients had between 1 and 5 new lesions (median = 3) with a wide intracranial distribution, consistent with an embolic source. Based on an examination by a non-neurologist physician, all patients were asymptomatic without overt neurological findings in the early aftermath of ablation, although sophisticated examination and testing were not performed. The use of cryoenergy was not immune to silent infarction, confirming prior results (5). The use of PVAC was the only factor predictive of new embolic events.

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From the Valley Heart and Vascular Institute, Columbia University College of Physicians & Surgeons, New York, New York. Dr. Steinberg is a consultant for Biosense-Webster, Medtronic, St. Jude Medical, Ortho-McNeil Jansen, Sanofi, and Stereotaxis, and has received research support from Biosense-Webster and Medtronic. Dr. Mittal is a consultant for Biosense-Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Medtronic, and St. Jude Medical, and has received research support from GlaxoSmithKline and Biosense-Webster.
The findings in this study are startling and raise 2 very important issues: 1) the safety of ablation for AF in regard to silent brain infarcts and its long-term clinical impact; and 2) whether newer alternative techniques have unexpected and potentially serious deleterious consequences.

It has only recently been recognized that an overt TIA or stroke likely represents only the "tip of the iceberg" when it comes to intracranial emboli resulting from catheter ablation of AF. MRI of the brain performed within the first few days of ablation can demonstrate clinically silent intracranial emboli in up to 14% of patients (6,7). Although a single embolic lesion is typically observed, some patients experience multiple emboli. Against this historical context, the observation in this study that a median of 3 new embolic lesions was observed in 37.5% of PVAC patients is even more alarming. The unresolved question is the clinical significance of these silent brain infarcts. In the present study, there was no control group, and neither repeat MRI nor neuropsychological testing was performed. Nonetheless, evidence suggests that these silent infarcts may not be benign. For example, in population-based studies, the presence of silent brain infarcts has been associated with worse performance on neuropsychological tests, a steeper decline in global cognitive function, and doubling of the risk of developing dementia (8). Patients must be informed of this risk and its uncertain consequences, and formal indications for the ablation procedure must weigh this risk, among others, relative to the very real symptom benefit for patients. It is imperative that new studies focus on very comprehensive, sensitive and reproducible neuropsychological testing, performed serially over at least several months and perhaps longer, in order to examine if, when, and to what extent these infarctions impact brain function. Serial MRI scans would help confirm the chronicity of the lesions. Only when armed with functional data can the medical and patient communities properly make a truly informed comparative assessment of treatment modalities for AF. It should be acknowledged, however, that AF alone can cause silent cerebral embolism (9), and superior suppression of AF versus other treatments by ablation may in fact produce a net benefit to patients, and thus controlled studies are critical. The final answers regarding consequences of these events may take many years to be fully understood.

Are these results so definitive that they have dealt a fatal blow to the new PVAC technology? The ethics committee prematurely terminated the study, so clearly these members felt convinced that patient safety was jeopardized. However, the small sample size means that the confidence intervals around the point estimate of embolic risk (not reported by the investigators) will be quite wide (true for all groups), making accurate risk assessment challenging. Thus, it is crucial to determine whether the findings reported by Siklody et al. (4) are reproducible with different investigators and centers, using larger samples. To this point, a very recent study by Gaia et al. has just reported virtually identical rates of silent cerebral embolism (including a several-fold higher rate for PVAC) when comparing the same modalities of ablation in 108 patients with paroxysmal AF (10). Although clinically apparent acute cerebral thromboembolic events do not appear to occur at a higher rate than expected (11,12), it is important to take a step back and ask whether the PVAC technology has incremental value versus alternative approaches. These 2 compelling recent reports indicate that this technology may have substantially greater risk than competing energy delivery systems, and it would be difficult to justify its use until greater clarification regarding mechanism and long-term consequences of silent cerebral embolism are clarified and addressed, or the findings are refuted.

What potential explanation underlies a several-fold increase in embolic events when using the PVAC catheter versus other techniques? Intuitively, restricting ablation deliveries to the fewest necessary to accomplish procedural goals is desirable (13); however, the PVAC and irrigated RF systems had similar cumulative energy levels. Procedure time is important because catheter dwell time in the left atrium exposes the patients to thrombus formation on ablation apparatus, air entry, and the inevitable variability in degree of anticoagulation. However, the PVAC patients had the shortest procedures. There is a nagging concern that reliance on duty-cycling and passive tissue cooling for prevention of thrombus formation and charring when no irrigation is applied during RF delivery may not in fact be accomplished routinely. Although, only a minority had visibly detectable material, there is no assurance that char or thrombus had not formed and already embolized, and it is not clear how diligent or meticulous was the search for material adherent to the catheter. The nature of the PVAC system promotes current density similar to conventional electrodes and power settings (11), which in turn may facilitate heating concentrated in small anatomic regions or heating of blood elements if tissue contact with the electrode is absent. It is unknown whether the materials of the PVAC ablation catheter or the manipulation during the procedure contributes to the risk as well.

The rates of silent embolic events for the irrigated RF catheter and cryoballoon are also higher than desirable. Should present-day practice change in any manner to take into account the risk of these events? We suggest the following initiatives.

1. It is a given that meticulous attention should be employed with respect to anticoagulation throughout the ablation process, including the sheath systems typically used. It may be valuable to test more intensive or customized (for ablation technique) anticoagulation regimens including higher activated clotting time targets, addition of antiplatelet medications, or use of the non-vitamin K antagonist anticoagulants as bridging or intraprocedure agents.
2. Catheter and ablation system designs should be thoroughly reassessed in the laboratory and with animal models to better understand by which mechanism these complications may occur, so that redesign could be undertaken if warranted.

3. The routine use of intracardiac ultrasound deserves further scrutiny as a means of early detection of thrombus before embolization (14).

4. Avoidance of intraprocedural cardioversion has been suggested (7).

5. It seems premature to require that all patients undergo pre- and post-ablation brain MRI, but a large-scale effort, probably via a multicenter registry, must be undertaken to more accurately depict the incidence, infarction pattern, and risk factors of embolic events independent of technique. One also wonders whether other left-sided atrial and ventricular ablations are associated with silent embolism as well.

6. It is possible that upstream filters may be required to prevent undesirable material from reaching the cranial circulation.

7. Finally, the inequality of distribution of events among the different ablation techniques strongly suggests that testing be part of the regulatory process before a new device or system reaches the market.

There is no question that AF ablation is an important therapeutic advance, but unintended consequences from complex invasive procedures should be thoroughly investigated and adjudicated. Our first and foremost concern must be both short- and long-term patient safety.

Reprint requests and correspondence: Dr. Jonathan S. Steinberg, Columbia University College of Physicians and Surgeons, 1111 Amsterdam Avenue, New York, New York 10025. E-mail: jss7@columbia.edu.

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