Ablation for atrial fibrillation is a commonly used therapeutic option for patients with refractory symptoms. However, initial optimism viewing ablative therapy as a safe, potentially curative treatment has been greatly tempered by reports of high recurrence rates and previously unrecognized complications.

Silent cerebral lesions (SCLs) are the newest complication to be described. In this issue of *Circulation Arrhythmia & Electrophysiology*, Rillig et al report their findings from their study of 70 patients undergoing atrial fibrillation ablation. They compared manual ablation with robotic intervention and found no difference in SCL between the groups (18% robot-assisted pulmonary vein isolation versus 15% manual pulmonary vein isolation). Although their study was likely underpowered to detect a difference between these groups, their and other recent reports have found a remarkably high incidence of SCL with various ablation techniques. Reactions from interventional electrophysiologists to these data have ranged from dismissing these findings as inconsequential artifacts to calls to reappraise the safety of endocardial atrial fibrillation ablation. Before the clinician can put Rillig et al’s data into perspective, we need to understand what we know of these detected signals, what they may represent, and whether they can be or need to be prevented.

What Are These Lesions?

With diffusion-weighted (DW) MRI, acute SCL was recognized as focal hyperintense signals with corresponding hypointensity in the apparent diffusion coefficient (ADC) maps. These findings represent cytotoxic edema from ischemia or infarction. Hyperintense signals with DW-MRI represent diffusion may occur within 30 minutes after vascular compromise, and the ADC continues to decrease for 8 to 32 hours.

The combination of markedly hyperintense lesions with DW imaging and associated hypointense ADC images, along with the fact that 2 independent blinded reviewers identified these signals, excludes artifact. Having established that the signals seen with DW imaging represent cytolytic edema, how certain can we be of ischemic origin? DW imaging is very sensitive (88%–100%) and specific (86%–100%) for detecting acute infarction. Although false-negatives may occur as a result of immediate reperfusion, false-positives are exceedingly rare and can be readily excluded (pyogenic abscess, tumor).

Thromboembolism

When clinical stroke occurs after left-sided ablation, thromboembolism is the usually diagnosed cause. Prior reports have shown a higher incidence of SCL with a nonirrigated duty-cycled ablation device than with standard irrigation. Because thrombus is less likely to form on the catheter with open irrigation has been considered. Furthermore, in the prior reports show that cooling the catheter tip clearly does not avoid SCL. The possibility that small thrombus does form but does not remain in the vicinity of the catheter from the open irrigation has been considered. Furthermore, in the present study, although the activated clotting times (ACTs) were maintained in an acceptable and recommended range (250–300 ms), most centers keep the ACT at ≈300 ms.

Cardioversion was shown in prior reports to increase SCL, but this correlation was not seen in the present study. Dislodgement of microthrombi with cardioversion was suggested as the etiology.

Coagulum

Heat-related denaturation of fibrinogen to fibrin (coagulum/char) is not a thrombin-mediated process and is thus prevented with adequate heparinization. Char formation is likely decreased with irrigation, but again because coagulum forms at the tissue interface and irrigation does not prevent tissue overheating, embolization of small coagular fragments remains possible.

Air Embolization

Air embolization is a well-described cause of ischemic brain injury. Potential sources for air in the systemic circulation

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From the Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, MN (K.L.V., S.J.A.); Department of Radiology, Columbia Asia Referral Hospital, Bangalore, India (J.E.H.); and the Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN (S.J.A.).

Correspondence to Samuel J. Asirvatham, MD, Division of Cardiovascular Diseases & Internal Medicine, Division of Pediatric Cardiology, Department of Pediatric & Adolescent Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, Tel: 507-293-3376, Fax: 507-255-2550, E-mail asirvatham.samuel@mayo.edu

(Circ Arrhythm Electrophysiol. 2012;5:2-4.)

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*Circ Arrhythm Electrophysiol* is available at http://circcep.ahajournals.org

DOI: 10.1161/CIRCEP.112.970509
include catheter exchange after transseptal puncture and sheath irrigation. Noteworthy is that in Rillig et al’s study,6 robotic navigation, which involves a larger sheath and necessity to flush both inner and outer sheathes, was not associated with a high risk of SCL. However, the small numbers in this study and thus risk of $\beta$ error may have resulted in the failure to note differences.

Ablation-related microbubble formation is another possible source of systemic air embolism.18,19 The exact cause of microbubbles is unknown and is likely multifactorial. Tissue overheating and boiling of cellular fluid produces in essence an endocardectomy “pop” occurs. Electrolysis even without heating (nonthermal direct current ablation) may also produce these bubbles, but the extent to which this occurs clinically with radiofrequency ablation is unknown. Furthermore, current cardiac version-related electrolysis being responsible for the excess SCL in prior reports has not been excluded.

**Hypoxia, Hypoperfusion, and Hypotension**

Notably the regions where SCL tend to occur (Table 3) are in the so-called watershed regions of the cerebral circulation, which are prone to injury with hypoperfusion. Transient right-to-left shunting after transseptal puncture and hypotension from anesthesia or induced arrhythmia, although globally decreasing cerebral circulation, may produce localized cytolytic edema from ischemia in these watershed regions.

**Why Do These Lesions Go Away?**

Rillig et al6 and others have shown that with follow-up imaging done in the majority of patients, the SCL were no longer seen. Does this tell us that the lesions were not a result of thromboembolism or that they are necessarily clinically insignificant?

In animal models of ischemia, a time as well as an ADC threshold for reversibility exists.20,21 Middle cerebral artery occlusion, <2 hours and/or when the ADC difference in value between ischemic and contralateral normal regions is not greater than $-0.25 \times 10^{-3}$ cm$^2$/s, is associated with complete resolution of the lesions. We do not know the exact ADC difference from the present study6 or prior reports, but we could assume that the reason for normalization is because of early reperfusion. Human case examples of complete reversibility are rare, but this may be due to the clinical context where DW-MRI is usually obtained (clinical stroke syndrome) where early and complete reperfusion is uncommon. However, even in patients with stroke and persistent clinical defects, ADC returns to baseline in 1 to 4 weeks. This likely represents continued cytotoxic edema and decreased diffusion balanced by vasogenic edema, increased extracellular water, and increased diffusion (pseudonormalization).9 Thus, the evidence of DW and ADC normalization is likely in the majority of patients from early relief of ischemia. Of the possible etiologies for the ischemic insult discussed previously, air embolization with spontaneous resorption appears to best fit this model.4

**If These Cerebral Lesion Are Silent, Were We Better Off Not Looking For Them?**

Rillig et al6 as well as in earlier reports of SCL, patients were asymptomatic and neurological examination normal. In the present series, 1 patient had a transient ischemic attack with left hemiparesis 2 days postablation that recovered. However, no SCL was detected 1 day prior. We do not know, however, if repeat DW imaging was done on this patient when symptoms occurred. Another patient presented with right arm transient paresis and had a left-sided SCL after ablation. However, repeat MRI showed no new or persistence of prior SCL, although we do not know the type of MRI performed or whether the time course excludes pseudonormalization, explaining the absence of findings. Clinical correlation with DW imaging is dependent on the location, size of the stroke, and acute ADC ratio.22,23 Although clearly all reported examples of SCL were relatively small and would not have been expected to be associated with major persistent neurological deficits, can we exclude less obvious clinical sequelae?

**Migraine**

An unexplained syndrome of new-onset migraine after atrial fibrillation ablation has been described.24 Similar etiologies including air, microthrombi, and hypoperfusion have been considered but remain conjecture. DW-MRI was not done in the patients with this reported syndrome.

**Neurocognitive Deficits**

Deficits in verbal memory have been demonstrated after pulmonary vein isolation.6 However, a clear correlation with findings on perfusion MRI was not demonstrated.

Whether routine perfusion and MRI in addition to careful objective assessment of atypical neurological symptoms and cognitive function will define the significance, if any, of SCLs is unknown.

**What Do We Do Now?**

At present we do not know whether DW-MRI-detected ischemic cytolytic (SCLs) are clinically significant or can be ignored. Rillig et al’s study,6 along with prior reports suggest that multiple etiologies may be responsible for these ischemic insults. Assuming multiple etiologies are present, should we consider alterations in our present ablation approach to minimize these small but present cerebral ischemic lesions? Sheath redesign (transseptal sheath redesign), meticulous air filtering, and choice of fluid and temperature may minimize passive air embolization. Care to avoid tissue overheating with better understanding of the limitations of temperature monitoring with open irrigation and techniques to prevent coagulum may help reduce both thromboembolic and air embolic events. Similarly, preferential epicardial approaches could also possibly minimize thrombotic and air embolic ischemic brain injury. Although clearly the lesions observed are small and to date no long-term sequelae have been established, we may need to remain cautious given the high percentage of these lesions being demonstrated in what are all relatively small studies done without routine detailed neurocognitive testing. We know from the early experience with coronary artery bypass surgery25,26 that it took years of accumulated data to establish detrimental neuropsychological impact and eventual positive change to bypass methods and improved patient outcomes.
In this report, Rillig et al. have added to our quickly increasing appreciation of previously unrecognized small but definite ischemic events that occur in our patients after atrial fibrillation ablation. Further study with routine multimodality imaging and neurocognitive testing will help us to understand whether we ignore this signal at our patient’s peril.

Disclosures
S.J.A. receives honoraria/consulting from Abiomed, Biotronik, Boston Scientific, Medtronic, Spectranetics, St Jude, Sanofi-Aventis, and Stereotaxis. He holds a patent and may receive future royalties from Nevro (use of nerve signal modulation to treat central, autonomic, and peripheral nervous system disorders, including pain), Aegis (appendage ligation), and ATP (atrial fibrillation ablation and coagulum reduction during ablation).

References

Key Words: Editorials ■ ablation ■ atrial fibrillation ■ cerebral lesions ■ MRI ■ stroke

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Malini Madhavan, Shalini R. Govil and Samuel J. Asirvatham

Circ Arrhythm Electrophysiol. 2012;5:2-4
doi: 10.1161/CIRCEP.112.970509

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