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Atrial Fibrillation and Stroke – Increasing Stroke Risk With Intervention

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Abstract

In this review, we focus on the important newly recognized appreciation for the paradoxical increase in stroke and TIA as a result of intervention meant to treat atrial fibrillation (AF) with the hope of decreasing stroke risk in the long term. The impact of silent cerebral lesions recently appreciated as a potentially major limitation and risk with AF ablation is explained. We categorize our present understanding of how we can minimize risk and provide a platform for what will undoubtedly be newer study, changes in the way procedures are done today, and possibly vascular-based stroke-reduction strategies.

Introduction

Atrial fibrillation is the most common sustained arrhythmia in adults, with an estimated prevalence of 2.1% in the United States.[1] Catheter ablation for atrial fibrillation (AF) is now commonly used in the management of patients with symptomatic drug refractory arrhythmias.[2] While increasingly successful approaches for ablation have become available over the last two decades, potential for complications remains a major impediment. Unfortunately, interventional procedures, including radiofrequency ablation, other ablation strategies, and indeed implanted cardiac devices, particularly in the presence of PFO may all represent an under-appreciated risk for stroke and TIA.[3] Although stroke is a well-recognized but rare complication of AF ablation, recent studies have shown an unexpected and alarming rate of silent cerebral lesions (SCL) detected by diffusion-weighted magnetic resonance imaging (MRI). The etiology and consequence of these lesions is currently the subject of intense research. We present the current state of our knowledge of the incidence, risk factors and potential significance of SCL and discuss techniques to prevent them.

Key Words:
Atrial fibrillation, Silent Cerebral Lesions, Ablation, Embolism, Catheter

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Abiomed, Atricure, Biotronik, Biosense Webster, Boston Scientific, Medtronic, Spectranetics, St. Jude, Sanofi-Aventis, Wolters Kluwer, Elsevier
Co-patent holder – may receive future royalties from:
Aegis: Appendage ligation
ATP: Atrial fibrillation ablation and coagulum reduction during ablation
Nevro: Use of nerve signal modulation to treat central, autonomic, and peripheral nervous system disorders, including pain
Sanovas: Lung ablation
Sorin Medical: Tricuspid valve project

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Silent Cerebral Lesions following AF ablation: Diagnosis, incidence and Risk Factors

Clinically evident stroke or transient ischemic attack (TIA) can be a devastating complication of AF ablation, but occurs in less than 1% of patients.[2,4] However, the use of post-ablation MRI of the brain has revealed the frequent occurrence of new lesions in the brain without clinically apparent stroke labeled as "silent cerebral lesions."[5-9] SCL is identified as focal, well- demarcated, hyperintense signals on diffusion weighted MRI with corresponding hypointensity in the apparent diffusion coefficient maps. These MRI findings represent cytotoxic edema due to ischemia or infarct and are very sensitive and specific for acute infarction.[10,11] Ischemic brain injury results in loss of membrane gradient and net movement of water into cells where movement is more restrained. The hyperintense lesions on the diffusion weighted MRI represent restricted diffusion of water in cells and appear within 30 minutes of the event. SCLs following AF ablation are frequently multiple occurring in several vascular distributions, again suggesting the embolic nature of these lesions.

The reported incidence of SCL varies from 4.3% to 38.9% depending on several procedural factors.[5,7,12,13] While the risk factors for SCL need further study, currently available data suggest that

procedural factors are more important than patient- related factors. The type of catheter and energy source has been the subject of several studies. The multielectrode PVAC catheter that delivers phased duty-cycled radiofrequency energy (Medtronic, MN) has been associated with higher risk of SCL compared to irrigated radiofrequency and cryoablation (38.9, 8.3 and 5.6% respectively).[7,13] However, no significant difference has been noted between irrigated radiofrequency catheter vs cryoablation[14] and mesh radiofrequency ablator vs cryoablation.[15] In another study, the number and design of external irrigation ports on the catheter did not affect the incidence of SCL.[16] A comparison between manual and robotic assisted radiofrequency ablation also did not reveal any differences.[8] Intra-procedure lower activated clotting time (ACT) and electrical cardioversion have been reported to be associated with a higher risk of SCL.[12,16,17] Ablation of complex fractionated atrial electrograms has been associated with increased risk in one study, but was not corroborated in another study.[17,18] Patient-related factors such as advanced age, persistent AF, lower left ventricular ejection fraction and spontaneous echo contrast on trans-esophageal echocardiography have been noted to be associated with SCL in some but not all studies.[14,17,18]

Irrespective of AF ablation, patients with AF are more likely to have silent cerebral ischemic lesions at baseline compared to patients in sinus rhythm.[19] A recent study from Gaita et al. demonstrated that paroxysmal and persistent atrial fibrillation patients had a higher prevalence and number of silent cerebral ischemic lesions per patient in comparison to those in sinus rhythm (89%, 92%, and 46% respectively, $p<0.01$).[19] Of clinical significance, the silent ischemic lesions in the AF group was associated with worse cognitive performance.[19]

There has been great interest in utilizing different MRI protocols to identify new procedure-related silent ischemic cerebral lesions such as T2-weighted spin echo sequence, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted (DW) echo spin protocols.[20] For example, DW-MRI allows detection of very small as well as acute ischemic lesions.[21] In addition, MRI is also able to reasonably differentiate between ischemic and embolic origins of brain lesions.[22,23] Small, sharply demarcated lesions, that are often in clusters, with bilateral distribution and located predominantly in the frontal lobe (the so- called "spotted pattern") strongly support an embolic mechanism typical of atrial fibrillation origination.[19]

Dynamic Assessment of Silent Cerebral Lesions Using TCD and ICE

Although MRI enables early detection of silent cerebral ischemic events, these lesions are not found until the ablation procedure is completed. A real-time assessment of emboli during ablation, with the potential to guide energy delivery, is paramount to improving overall ablation procedural safety. Two methods have been used for this purpose: 1) monitoring for the formation of microbubbles on intracardiac echocardiography (ICE), and 2) detection of microembolic signals (MES) in the cerebral arteries by transcranial Doppler (TCD). Kilicaslan et al. first reported on MES detected by TCD during pulmonary vein isolation, finding a close correlation between MES and the amount of microbubble formation detected by ICE.[24] Future research must focus on the correlation between MES on TCD and the occurrence of SCL on MRI as well as long term neurological outcome before this technology finds widespread use in AF ablation.

Silent Cerebral Lesions: Significance and Long-Term Follow-Up

While silent cerebral lesions in patients with AF are associated with cognitive decline,[19] whether SCL after AF ablation leads to long term cognitive dysfunction is not well understood. Investigation of mild neurocognitive effects of SCL have so far focused on short-term outcomes. Medi et al. recently reported higher prevalence of cognitive dysfunction based on neuropsychiatric testing with an incidence of 28% in paroxysmal AF and 27% in the persistent AF ablation groups (compared to the non-ablative group in which no patients developed cognitive dysfunction).25 These findings occurred at 24 to 48 hours after the procedure and remained significant in the ablative compared to the control groups at 90 days (13% paroxysmal, 20% persistent AF, 0 in non-ablative group).[25] The data become even more striking when taking into account the fact that the majority of patients included in the study had low $CHADS_2$ scores (0-1). Similarly Schwartz et al. showed decline in verbal memory 3 months following AF ablation.[26] In contrast, Haeusler et al. did not note any change in cognitive function in the post-ablation period despite a 40% incidence of new SCL.[15] It must be noted that these studies utilized different tools for neuropsychiatric assessment which can influence the findings significantly.

Despite the high incidence of cerebral lesions after ablation, current data suggest that the majority of these resolve in the long-term without discernible changes on MRI. In a long-term follow-up study of 9 patients with new silent cerebral infarcts post AF ablation, there was an attenuation of radiological lesions over time with no residual lesions seen on repeat MRI after 21 months.[8] Similarly, Deneke at al. demonstrated that 94% of asymptomatic lesions resolved at about 1 year post-ablation, with only larger (>10 mm) acute lesions producing chronic glial scars at long-term follow-up.[5] This finding was also confirmed by a study using 3 Tesla MRI, enabling a much higher contrast-to-noise ratio and improving diagnostic reliability of ischemic lesion detection.[15] In light of these findings, there is much research that remains to fully characterize the long term neurological effects of these resolved lesions.

Etiology of Silent Cerebral Lesions During Ablation and Techniques to Reduce Incidence

Several factors can cause silent ischemic lesions and these may co-exist during ablation procedures.[27] The proposed mechanisms involved include (1) thromboembolism, (2) air embolism, (3) coagulum formation, and (4) hypoperfusion or hypoxia.[28,29] Several recent studies have focussed on the potential etiology of SCL and techniques to reduce the risk. In addition to the major factors involved in generation of this embolic phenomenon, we review the relevant considerations that have been studied to date in an attempt to reduce the incidence of these lesions.

Thromboembolism

Thromboembolism is often diagnosed as the etiology of stroke in patients with atrial fibrillation including following ablation procedure. Similarly thromboembolism has been proposed as an important cause of SCL after ablation. Thrombus can form on the catheter, sheath, or ablated endocardial surface during ablation. The risk of thrombus formation is modulated by several procedural factors including anticoagulation, type of catheter, energy source for ablation and cardioversion during the procedure. These factors each lend an

opportunity to reduce the risk of SCL.

Heparinization: Robust Activated Clotting Time Goal

Heparin use during AF ablation should in theory limit or reduce formation of thrombus while ablating in the left sided circulation. Ren et al. investigated the effects of heparin in trying to reduce left atrial thrombus formation through a robust activated clotting time (ACT) goal of >300 (301-400) s compared to 250-300 s during AF ablation.[30] The authors found a significant difference in the higher intensity ACT (>300) group with respect to a lower incidence of left atrial thrombus in patients with spontaneous echo contrast (SEC).[30] This led them to conclude that patients with SEC may benefit from more aggressive ACT goals during AF ablation procedures.[30] Consistent with these findings, Scaglione et al. found that a high intra-procedural mean ACT value was the only independent protective factor against thromboembolic lesion formation in patients undergoing AF ablation.[16] Furthermore, in fitting with the positive correlation between a more aggressive heparinization strategy and lower embolic risk, Scaglione et al. found that an incremental increase of 1s in ACT was associated with a decreased risk of 0.4% in developing silent embolic lesions during catheter ablation.[16] The risk of spontaneous echo contrast is also an independent predictor of cerebral embolic lesions despite the continued use of oral anticoagulation.[17,31]

Heparinization: Importance of Timing

In addition to an adequate heparinization strategy, the timing of heparin administration is crucial. Bruce et al. found that administration of heparin prior to transseptal puncture was critical in reducing left atrial thrombus formation during ablation procedures.[32] Moreover, this early heparinization approach did not increase the risk of bleeding complications.[32]

Current guidelines on catheter ablation of atrial fibrillation recommend an ACT goal of 300 – 400 s and administration of heparin before or soon after transseptal puncture.[2] We prefer the administration of heparin prior to transseptal puncture.

Peri-Procedural oral Anticoagulation

The continuation of therapeutic warfarin anticoagulation during AF ablation has been proposed to reduce the risk of thromboembolism and bleeding complications related to vascular access. Verma et al. recently reported a lower incidence of SCL with the use of multi-electrode duty-cycled phased RF ablation with the institution of several procedural changes including the continuation of therapeutic oral anticoagulation during the procedure.[33] However, the continuation of warfarin during the procedure does not abolish the risk of SCL in another study, with 12% of patients experiencing SCL during open- irrigated catheter ablation on therapeutic anticoagulation.[17] Data on the safety and efficacy of continuation of newer oral anticoagulants during AF ablation is lacking.

While the timing and intensity of heparin anticoagulation during the procedure and peri-procedure anticoagulation can lessen the risk of thromboembolic events during AF ablation, they are not adequate to prevent all events. This highlights the importance of sources of embolism apart from thrombi during the ablation procedure such as air and coagulum discussed below.

Air Embolism

Air embolism has been proposed as a potential etiology for SCL based on observations in animal models and human studies. Potential sources of air embolism include 1) catheter exchange after transseptal puncture, 2) irrigation of sheaths, and 3) microbubble formation during ablation.

Haines et al. reported both particulate and air embolism detected in an extracorporeal circulation during ablation in a swine model.[34] Furthermore, in another elegant proof of concept study, they showed that injection of air or coagulum into the carotids caused MRI- detected lesions that were reflective of what was seen on histologic review at autopsy.[35] Studies in humans using intracardiac echocardiography (ICE) imaging and transcranial Doppler for monitoring of cerebral microembolic signals have shown a correlation between microbubbles during ablation and cerebral emboli during radiofrequency ablation with both irrigated and non-irrigated catheters.[24,36] These studies suggest that the majority of microemboli are gaseous in nature. Furthermore, non-irrigated multielectrode catheters resulted in more microbubbles compared to the open irrigated catheter.[24,36] The exact cause of microbubbles during radiofrequency ablation is not known. Potential causes include tissue heating leading to an endocavitary 'pop' and electrolysis. Wood et al. have suggested that during RF ablation application, once the presence of microbubbles are seen, it may be prudent to cease RF energy or slowly decrement energy in order to prevent propagation of microbubbles further.[37] Kilicaslan et al. further demonstrated that the titration of radiofrequency energy output to minimize microbubbles detected by ICE can reduce the number of microembolic signals and symptomatic neurological events.[24] This technique warrants further study and validation.

Air embolism can also occur during catheter exchange through the transseptal sheath and with irrigation of sheaths. Air can also be introduced into the sheath during introduction of a catheter. Catheters with a more complex design such as circular and cryoballoon catheters are more prone to this compared to catheters with a smooth bullet shaped tip. Furthermore, sheaths with a lumen introduced into the left atrium can be more thrombogenic than a solid catheter, increasing the risk of thromboembolism.[38,39] Meticulous attention should be paid to management of the sheath to minimize these complications. The sheath should also be maintained on a continuous flush of normal saline. Cauchemez et al. showed that a high flow continuous flush at 180 ml/hr is more effective than a low flow flush at 3ml/hr in preventing clinical stroke.[38] Rapid withdrawal of the catheter through the sheath can cause aspiration of blood into the tip of the sheath predisposing to thrombus. All catheter exchanges must be performed slowly during continuous flushing of the sheath. Catheter introduction under submersion should also be considered, especially for catheters with complex geometry. Many operators withdraw the long transseptal sheath into the right atrium during catheter manipulation in the left atrium.[40]

Coagulum Formation

The risk of embolic showering during atrial fibrillation ablation procedure can result from formation of coagulum.[41] Coagulum forms due to heat-induced denaturation and aggregation of components of the fibrin clot (platelets, red blood cells, and most notably fibrin) at the electrode – tissue interface.[41,42] The use of irrigated tip catheters has significantly reduced the risk of coagulum formation.[43] The critical part in the pathway to coagulum formation is electrostatic conformational changes in fibrinogen polymers and the subsequent attachments of these aggregates to the catheter surface.[41] Lim et al.

have shown that applying a negative charge to the catheter surface prevents aggregation of these fibrogen polymers, and thus provides an innovative technique to reduce coagulum formation.[41]

Hypotension, Hypoxia and Cerebral Hypoperfusion

While embolism is considered the major cause of SCL, infarction in watershed regions of the brain due to hypoperfusion cannot be ruled out. Several procedural factors predispose to hypoperfusion and hypoxia, including hypotension from anesthesia and arrhythmia induction and transient right to left shunting across the transseptal puncture. Measures should be taken to prevent hypotension during the procedure.

Impact of Energy Source and Catheter Design on SCL

Observational studies have shown significant differences in rate of SCL between various catheter designs and energy sources as discussed previously. The use of saline irrigation of catheters for active cooling of the catheter tip can reduce the risk of thrombus and coagulum formation on the catheter.[43] Furthermore, open irrigation tip catheters have been shown to be more effective in reducing coagulum formation than internally cooled catheters in a swine model.[43]

The non-irrigated multielectrode duty-cycled phased radiofrequency ablation catheter (PVAC) has been particularly associated with a high risk of SCL; as high as 38%.[7,13] Observations from swine and human studies with the PVAC catheter are instructive in understanding the combination of factors that lead to SCL.[34] The PVAC is a decapolar non-irrigated catheter capable of duty-cycled unipolar-bipolar radiofrequency ablation. Although duty cycling and phasing of RF delivery is expected to allow periodic cooling of the tissue catheter interface, clinical studies showed a higher incidence of SCL with this catheter. The following mechanisms have been proposed to explain the higher risk of SCL with the PVAC catheters: 1) the multipolar catheter design can result in variable tissue contact on each electrode predisposing to overheating of some poles and coagulum formation;, 2) the lack of external irrigation may result in variable cooling of each electrode by blood flow;, 3) the complex catheter geometry can result in air embolism during introduction across the hemostatic valve;, and finally 4) excessive microbubble formation during accidental overlap of electrodes 1 and 10 on the catheter due to shunting of excess current density and overheating.[7,13,34] Verma et al. showed that meticulous attention to prevent these factors can significantly reduce the risk of SCL with PVAC ablation.[33] The authors systematically introduced 3 procedural changes: 1) either electrode 1 or 10 was deactivated to prevent accidental bipolar interaction;, 2) introduction of the catheter into a introducer under saline to prevent ingress of air;, and 3) therapeutic anticoagulation with warfarin and heparin to maintain ACT > 350ms. These measures resulted in a reduction in rate of SCL to 1.7% with use of the PVAC catheter.

The use of cryoablation in order to limit thermal injury of tissue at catheter contact interface has been evaluated for potential to reduce embolic lesions during ablation. Although histopathological studies have shown a lower risk of endocardial thrombus formation with cryoablation compared to RF, this has not been borne out in clinical studies which have shown a similar rate of SCL with the cryoballoon and irrigated RF catheter.[7,14,28] This may be explained by microemboli and air emboli introduced by multiple catheter manipulations and thrombus formation at the catheter sheath interface. Sauren et al. reported fewer microembolic signals using TCD during cryoablation compared to RF ablation. However, the majority of emboli with cryoablation occurred during catheter manipulation and at the end of each cryoablation in contrast to radiofrequency ablation which produced microemboli predominantly during energy delivery.[44]

Recent Studies, Remaining Challenges, and Future Considerations

Benefits of Catheter Ablation in Patients with AF

Recent findings discussed above should create pause and a re-assessment of the risks associated with AF ablation. However, these findings should also be interpreted in light of the potential benefits of AF ablation. Bunch et al. demonstrated that patients who have undergone AF ablation had a lower long term incidence of stroke compared to patients who have not undergone an ablation procedure.[45] This data held true even after stratifying for baseline propensity for stroke using $CHADS_2$ scores, as well as comparing for stroke across age groups.[45] In a prior study from the same authors, findings of reduced stroke, dementia, and mortality were found in patients who underwent AF ablation compared to those with AF who did not undergo ablation.[46]

Need for Future Studies and Innovation

The issue of embolic lesions occurring during catheter ablation of AF is real. While several recent studies have shined a light on the magnitude of the problem and potential solution, several questions remain unanswered. Future studies should focus on better defining patient- and procedure- related factors that affect the incidence of SCL and the true pathogenesis of these lesions. Longer term follow-up of patients with SCL after ablation and assessment of impact on neurocognitive function are required to better understand the true impact of these lesions. Finally, innovative strategies are needed to significantly reduce the risk of cerebral embolism. These innovations can take the form of better anticoagulation strategies, radically different approaches to AF ablation, or exploration of cerebral protection strategies including devices.

As the new age oral anticoagulants continue to pervade practice , future studies evaluating for safety analysis to balance potential reduction in embolic lesions associated with ablation, with the risk of increased bleeding are needed.[47] A large number of studies[48-54] have been conducted looking at such drugs as dabigatran and warfarin peri-procedurally to reduce embolic complications from left- sided ablation, while also assessing for hemorrhagic complications. A recent editorial called for a prospective trial including one of the newer anticoagulants to assess for silent cerebral lesions during AF ablation.[47]

An entirely epicardial approach to AF ablation can eliminate the risk of cerebrovascular accidents associated with endocardial ablation. Sauren et al. reported reduced incidence of cerebral microembolic signals during thoracoscopic epicardial pulmonary vein isolation compared to percutaneous endocardial ablation.[55] However, currently available strategies for epicardial ablation are significantly invasive, making them undesirable for the majority of patients. Future innovations focussed on minimally invasive percutaneous epicardial ablation are required. The use of carotid protection devices in patients with thrombus during ablation has been reported in individual cases.[56] However, currently available devices are riddled with problems such as a pro-thrombotic tendency, prohibiting the wide spread use of these devices. Future technical innovations in the field of cerebral

protection are needed.

Conclusions:

In summary, MRI detected silent cerebral lesions that occur during atrial fibrillation ablation are indeed real and pose serious risks and challenges. Further prospective trials with longer follow up periods are required to increase our understanding in how best to risk stratify patients who are candidates for atrial fibrillation ablation. To achieve improved ablation safety, the future of the field must find itself taking a multidisciplinary and multi-modal approach in determining the best method to prevent these lesions. This will involve innovation in ablation techniques, anticoagulation and cerebral protection.

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