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A Patient With Asymptomatic Cerebral Lesions During AF Ablation: How Much Should We Worry?

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Abstract

Silent brain lesions due to thrombogenicity of the procedure represent recognized side effects of atrial fibrillation (AF) catheter ablation. Embolic risk is higher if anticoagulation is inadequate and recent studies suggest that uninterrupted anticoagulation, ACT levels above 300 seconds and administration of a pre-transeptal bolus of heparin might significantly reduce the incidence of silent cerebral ischemia (SCI) to 2%.

Asymptomatic new lesions during AF ablation should suggest worse neuropsychological outcome as a result of the association between silent cerebral infarcts and increased long-term risk of dementia in non-ablated AF patients. However, the available data are discordant. To date, no study has definitely linked post-operative asymptomatic cerebral events to a decline in neuropsychological performance. Larger volumes of cerebral lesions have been associated with cognitive decline but are uncommon findings acutely in post-ablation AF patients. Of note, the majority of acute lesions have a small or medium size and often regress at a medium-term follow-up.

Successful AF ablation has the potential to reduce the risk of larger SCI that may be considered as part of the natural course of AF. Although the long-term implications of SCI remain unclear, it is conceivable that strategies to reduce the risk of SCI may be beneficial.

Introduction

Catheter ablation (CA) is a recognized treatment for patients with symptomatic atrial fibrillation (AF) refractory to drug therapy.[1-6] However, the complexity of the procedure may expose patients to a considerable number of complications.[7-10] Stroke and thromboembolisms are among the most worrisome periprocedural complications following left atrial (LA) catheter ablation. Recent evidence suggests that clinically apparent cerebral ischemia is only the "tip of the iceberg" because an higher than expected rate of subclinical cerebral emboli can be detected by imaging after LA ablation, opening up a discussion about their clinical relevance and how to reduce them.[11]

Key Words:
Asymptomatic Cerebral Embolism, Silent Cerebral Ischemia, Atrial Fibrillation Ablation, Magnetic Resonance Imaging, Stroke.

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None.

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Clinical thromboembolic events after AF ablation typically occur within the first 24h of the procedure with a high-risk period extending for the first 2 weeks.[12] Periprocedural stroke incidence rate has been estimated to be between 0.1 and 0.8% in AFCA patients, and a similar incidence rate has been observed for periprocedural transient ischemic attacks (TIA).[11-13] Surprisingly, it is becoming increasingly evident that AF ablation may cause silent ischemic lesions (Figure) in up to 40% of the cases.[11,14] The incidence of periprocedural silent ischemic lesions varies considerably, depending upon several factors among which the ablation procedure and periprocedural anticoagulation strategy play a pivotal role.

Mechanisms and Procedure Related Risk Factors of Periprocedural Brain Lesions

Thrombus formation during and after LA ablation might result from platelet and coagulation system activation either directly at the catheter surface or at the site of endothelial application. Additional potential mechanisms may account for the risk of silent cerebral ischemia (SCI) associated with AFCA. Air microemboli may be introduced into the blood stream through sheaths and catheters

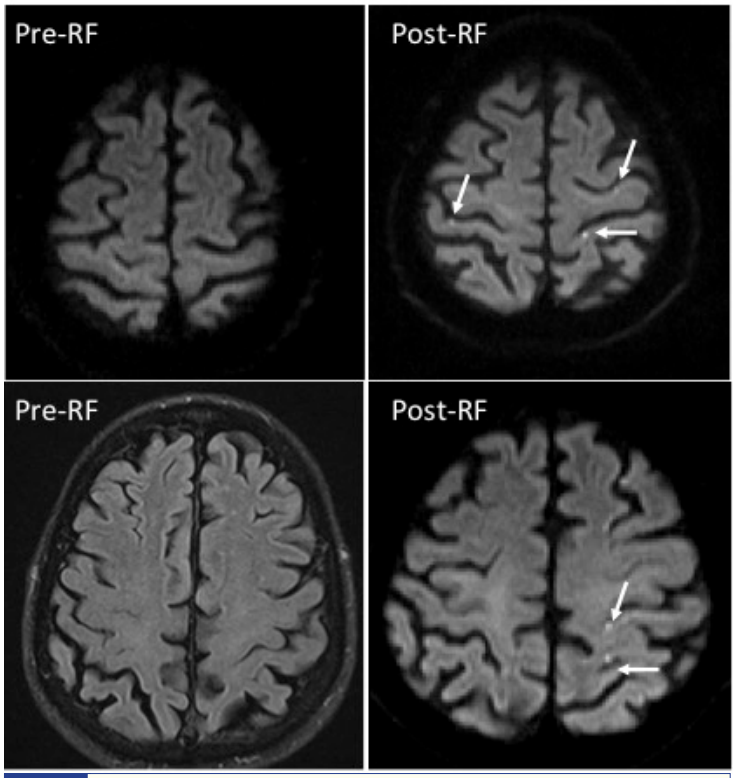

Figure:1 **Selected MR-images from a patient, displaying small and clinically silent ischemic lesions (indicated by arrows) detected 2 days after the ablation procedure.**

or developed during ablation as a result of blood boiling during radiofrequency catheter ablation.[15] Furthermore, a residual iatrogenic atrial septal defect after trans-septal puncture might increase the risk of paradoxical embolism. However, recent evidence suggests a high sealing rate of the defect (66%) immediately after the procedure and a very low incidence of persisting inter-atrial shunt (4-7%), predominantly left-to-right, at 12 months of follow-up[16-17] which is not associated with an increased risk of symptomatic cerebral/systemic embolism.

The source of ablation energy may play an important role in the genesis of periprocedural brain lesions. Most ablation procedures are being performed with closed- or open-irrigation radiofrequency energy (RF) catheters, which are capable of focal ablations. Balloon and coil platforms, using different energy sources, are being tested as potential alternatives for focal RF catheters, with the hope to optimize efficacy and minimize complications.[18-22] Cryo-balloon PV isolation is promising because of the low thrombogenicity and the lower risk of PV stenosis. Results from clinical studies showed that the use of cryoablation for pulmonary vein isolation (PVI) is associated with a low risk of endothelial disruption, thrombogenicity, and pulmonary vein stenosis compared to RF ablation.[23,24] Sauren et al. have analyzed the incidence of cerebral microembolic signals via transcranial Doppler monitoring in patients undergoing PVI with three different ablation procedures: segmental PVI using a conventional radiofrequency ablation catheter, segmental PVI using an irrigated radiofrequency tip catheter and circumferential PVI with a cryoballon catheter.[25] When compared to an irrigated radiofrequency tip catheter and a cryoballon catheter, the use of a conventional radiofrequency catheter for PVI was associated with a significantly higher incidence of cerebral microembolic signals. Other brain magnetic resonance imaging (MRI) studies showed a similar risk of SCI between open-irrigated RF and cryoballoon technologies.[26-27]

In contrast, the risk associated with phased RF multi-electrode catheters (PVAC) has been consistently higher than other forms of ablation energy.[28-30] In order to reduce the thromboembolic risk of PVAC technology, Verma et al.[31] recently demonstrated in 60 patients undergoing PVAC ablation that the use of three specific procedural interventions (ACT >350 seconds with uninterrupted oral anticoagulants (OAC), underwater loading, distal or proximal electrode deactivation to prevent overlapping) significantly reduces the SCI incidence to 1.7%.

Other procedure-related factors linked to an increased risk of subclinical cerebral lesions are additional LA substrate ablation (e.g. adjunctive ablation at sites exhibiting complex fractionated atrial electrograms), regardless of LA time (time spent with catheters in the LA) and the occurrence of intraprocedural cardioversion.[32] Cardioversion during AF ablation might increase the risk of clinically evident and silent embolism. Specifically, emboli can be released from LA after sinus rhythm restoration as well as impaired LA diastolic function following cardioversion may promote thrombus formation in the LA appendage. Although data are still inconsistent, the incidence of silent cerebral lesions seems to be lower in patients remaining in stable sinus rhythm throughout ablation than in patients undergoing periprocedural cardioversion. A recent study has reported a 2.75-time increase in the risk of subclinical cerebral embolism related to periprocedural cardioversion.[11] Analogously, Ichiki et al.[33] found that the use of cardioversion during the procedure was the most important predictor of cerebral thromboembolism after AF ablation (OR, 3.31). In this perspective, it would be worth trying to restore sinus rhythm with catheter or postponing cardioversion until after the procedure once atrial lesions are healed.[11] However, the question has to be resolved yet because the association between brain lesions and periprocedural cardioversion was not as evident in a few studies.[34-36]

Periprocedural Anticoagulation: New Data, Still Open Questions

It is still unclear which is the best anticoagulation approach to reduce the incidence of neurological sequelae during AF ablation. Embolic risk is higher if anticoagulation is inadequate and concerns underscore the importance of uninterrupted anticoagulation in the peri-ablation period. In a large, high-risk patient population, the COMPARE trial has recently demonstrated that performing catheter ablation of atrial fibrillation without warfarin discontinuation reduces the occurrence of peri-procedural stroke/TIA.[37] Periprocedural symptomatic thromboembolic events occurred in 39 patients (4.9%) off-warfarin and in 2 patients (0.25%) without warfarin discontinuation. Therefore warfarin discontinuation had a ten-fold higher chance of cerebral thromboembolism. In the light of these results, it is noteworthy that published studies that investigated MRI-detected brain lesions after AF ablation included a range of anticoagulation strategies that may not reflect the current best practices (Table 1). Indeed, in most of these studies patients had warfarin discontinuation before the procedure. It is plausible that keeping patients on continuous OAC, as opposed to interrupted anticoagulation, protects against the risk of periprocedural silent brain infarcts, and warrants further investigation.[36] Di Biase et al.[36] demonstrated that performing AF ablation with "therapeutic INR" and pre-transseptal catheterization

Table 1: Published studies evaluating the incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation

Study (Reference)	Patients (n)	AF type	Periprocedural anticoagulation, %	Technology used for LA ablation	Silent Strokes
Lickfett et al. 2006[61]	20	paroxysmal	OAC held with bridging	Irrigated RF (PVI only)	10%
Gaita et al. 2010[11]	232	59% paroxysmal 41% persistent	OAC held with bridging	Irrigated RF (PVI, lines and CFAE ablation)	14%
Schrickel et al. 2010[14]	53	89% paroxysmal 11% persistent	OAC held with bridging	Irrigated RF (PVI only)	11%
Herrera et al. 2011[28]	74	paroxysmal	OAC held with bridging	Irrigated RF/Cryo/PVAC (PVI only)	37,5% (PVAC) 4.3% (cryoballoon) 7.4% (irrigated RF)
Gaita et al. 2011[29]	108	paroxysmal	OAC held with bridging	Irrigated RF/Cryo/PVAC (PVI only)	38.9%(PVAC) 8.3%(irrigated RF) 5.6%(cryoballoon)
Deneke et al. 2011[59]	86	64% paroxysmal 36% persistent	OAC held with bridging	Irrigated RF/PVAC (PVI only)	38%
Neumann et al. 2011[26]	89	81% paroxysmal 19% persistent	OAC held with bridging	Irrigated RF/Cryo (PVI, lines)	8.9% (Cryoballoon) 6.8% (irrigated RF)
Scaglione et al. 2012[62]	80	paroxysmal	OAC held with bridging	Irrigated RF (PVI only)	6%
Ichiki et al. 2012[63]	100	50% paroxysmal 50% persistent	Uninterrupted OAC	Irrigated RF (PVI/CFAE ablation)	7%
Martinek et al. 2013[32]	131	60% paroxysmal 40% persistent	Uninterrupted OAC	Irrigated RF (PVI, lines and CFAE)	12%
Schmidt et al. 2013[27]	99	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	22%
Ichiki et al. 2013[33]	210	53% paroxysmal 47% persistent	Uninterrupted OAC/Dabigatran	Irrigated RF (PVI/CFAE ablation)	12%
Haeusler et al. 2013[35]	37	paroxysmal	OAC held with bridging	PVAC (PVI only)	41%
Wieczorek et al. 2013[58]	37	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	27%
Verma et al. 2013[31]	60	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	1.7%
Di Biase et al. 2014[36]	146	26% paroxysmal 32% persistent 42% Long-standing persistent	Uninterrupted OAC and heparin bolus pretranseptal puncture	Irrigated RF	2%

Abbreviations: OAC=oral anticoagulants; RF= Radiofrequency; PVI= pulmonary vein isolation; PVAC =phased RF multi-electrode catheters

intravenous heparin bolus with ACT > 300 seconds significantly reduces the prevalence of SCI (2%) compared to patients off warfarin and those non-compliant with the anticoagulation protocol. Similarly, Verma et al showed that new post-procedural SCI occurred in only 1.7% of patients undergoing AF ablation with therapeutic INR and ACT > 350 seconds.[33]

A recent study[38] confirmed that an aggressive anticoagulation strategy during RF catheter ablation (ACT >320s) reduces the number of microembolic signals on transcranial Doppler compared to a conventional one (ACT >250s). Of note, this study showed that the majority of microemboli during AF ablation are gaseous or non-thrombotic particulate debris, regardless of the technology and the anticoagulation strategy; as a consequence, their occurrence cannot be reduced with aggressive anticoagulation.

Vitamin K antagonists (VKA) have been the standard of care for stroke prevention in AF patients for decades. Multiple new oral anticoagulants (NOACs) have been developed as potential replacements for VKAs for stroke prevention in AF. These newer agents have been demonstrated to be non-inferior to VKAs in many treatment areas and have become available as an alternative to VKAs for prevention of thromboembolism. With the increasing use of these agents, several key issues have also emerged. The feasibility and safety of periprocedural newer anticoagulants in AF ablation have been controversial in several previous studies.[39-43] Ichiki et al.[33] compared the incidence of asymptomatic cerebral microthromboembolism between warfarin therapy and dabigatran therapy in 210 consecutive patients undergoing AF ablation. New microthromboemboli were detected in 10.0% of patients undergoing AF ablation with uninterrupted warfarin versus 26.7% of patients with perioperative dabigatran therapy ($P < 0.05$) Similarly, Dentali et al. reported that the incidence of symptomatic cerebral thromboembolism after AF ablation was higher in the dabigatran group than in the warfarin group.[43] On the other hand, Kaseno et al. reported that the incidence of symptomatic and asymptomatic cerebral thromboembolism after AF ablation was comparable in the dabigatran and warfarin groups.[42] In addition it is important to note that to maintain ACT levels above 300 seconds during the AF ablation procedures, a higher amount of heparin is needed both for factor II and factor Xa inhibitor when compared to warfarin.[44]

Data on NOACs are still conflicting and further evaluation is needed to optimize safety profile of these novel anticoagulants.[45-48] Current evidence suggests that Dabigatran therapy may not be an effective alternative to periprocedural warfarin therapy in AF ablation, especially in patients who undergo cardioversion during the procedure. The role of the newer oral anticoagulants in AF ablation requires further investigation in high risk patients and should be compared to continuous on warfarin treatment. Very recently, the VENTURE-AF trial demonstrated that the use of uninterrupted

oral rivaroxaban was feasible in patients undergoing AF ablation and event rates were similar to those for uninterrupted VKA therapy.[49]

Subclinical Brain Lesions and Cognitive Dysfunction: The Sound of Silence

Clinically evident stroke is not the only neurological consequence of AF. Atrial fibrillation adversely impacts neurocognitive function, and it is associated with all forms of dementia, including Alzheimer's disease.[50] Multiple studies have demonstrated an increasing association between AF and cognitive impairment. This association was first observed in the Rotterdam study,[51] a large cross-sectional, population-based study, which reported an age- and sex-adjusted odds ratio for dementia and impaired cognitive function of 2.3 (95 % confidence interval, 1.4-3.7) and 1.7 (95% confidence interval, 1.2-2.5), respectively. Interestingly, the authors observed that this association was present even if no clinical stokes have occurred. Bunch et al. in their retrospective study of 37,000 patients showed that AF patients younger than 70 years were at the greatest risk of premature dementia.[50]

Silent brain infarcts assessed by brain MRI may be associated with dementia and cognitive decline.[52-54] Prevalence of silent cerebral infarction on MRI in AF patients varies between 5.8% and 28.3%. For example, Cha et al. found silent strokes in 28.3 % of AF patients compared to 6.6 % for non-AF patients.[55] In a population-based study that enrolled 15000 patients Vermeer et al[52] showed that the presence of silent brain infarcts on MRI at baseline doubled the risk of dementia in the general population. The infarcts were more often located in the basal ganglia (52%), followed by other subcortical and cortical areas.[56] Age, size, severity, and location of the brain lesion might also influence the onset and severity of dementia.[57] Elderly patients might be more vulnerable to cognitive decline due to lower cortical volumes.

Asymptomatic Cerebral Events During AF Ablation: Do not Worry, It is Not all Worrisome

Brain MRI has identified a high incidence of acutely detected ischemic embolic lesions after catheter ablation of AF (Table 1).[11,14,28,29,35,58-63] Whether post-operative silent cerebral infarction results in cognitive dysfunction is not well established. Asymptomatic ischemic cerebral lesions have been documented by diffusion-weighted MRI after many invasive cardiac procedures. Sauren et al[25] found 3,908 +/- 2,816 (mean,SD) microembolic signals within the basal cerebral arteries during AF ablation; this number is comparable to patients subjected to major cardiac surgery and suggests that neuropsychological change, probably similar to major cardiac surgery, can be expected during the catheter ablation process.

Several studies evaluated the prevalence of post-operative cognitive dysfunction in patients after RF ablation for AF. Medi et al. showed that AF ablation is associated with a 13% to 20% prevalence of post-operative cognitive dysfunction that persists at 90 days after the procedure.[64] Increased LA access time was significantly associated with post-operative cognitive dysfunction on univariable analysis. Schwarz et al.[65] compared the results of neurocognitive testing of 21 patients undergoing AF ablation with those of 23 non-AF controls. Overall, 56.5% of patients who underwent ablation deteriorated from baseline on the verbal memory tests, compared with 17% of controls. Interestingly, in this study the decline was not explainable by evidence of micro embolic lesion as detected on MRI; it is possible that decline in cognitive functions is multifactorial and not correlated to focal lesions only.

Very recently Madhavan et al.[66] performed neuropsychological testing in 28 patients before and after AF ablation. No correlation between SCI and cognitive decline was noted. These data indicate no relevance of the small number of SCI produced during ablation to neurocognitive dysfunction. Similarly, the association between post-operative silent cerebral infarction and dementia was not evident in other studies.[35,59,67] Irrespective of the severity of periprocedural stroke, Patel et al. reported a complete functional and neurocognitive recovery over 38.4 ± 24 months of follow-up, in most patients who had an acute cerebrovascular event secondary to AF ablation.[67] Notably, Vermeer et al[52] showed that the risk of cognitive decline is confined to people who had additional silent brain infarcts during follow-up. AF patients continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function. It would be logical to think that successful AF ablation may attenuate the risk of developing dementia by reducing the risk of subsequent brain infarcts. To date, no study has definitely linked post-operative MRI brain lesions to decline in neuropsychological performance. Furthermore, only limited knowledge on the histopathological significance of MRI-detected brain lesions exist.

Notably, the majority of acute MRI lesions observed after AF ablation regress without evidence of chronic glial scar when reassessed at short-term follow-up.[32,59,68] Post-ablation lesions might recognize different histopathological mechanisms compared to the lesions documented in patients naïve to LA interventions. MRI-detected brain lesions might be the common imaging endpoint of different mechanisms including thrombus, air, tissue or fat embolism during an AF ablation procedure. Micro-embolic lesions related to air embolism may cause less brain damage compared to solid embolic events. The mechanism of brain signals in non-ablated AF patients remains still unclear but may be due to small haemorrhagic infarcts and/or small embolic infarcts.

Deneke et al. evaluated the clinical course and longer-term characteristics of post-ablation MRI detected asymptomatic cerebral lesions.[59] In post-ablation MRI, 50 new brain lesions were identified in 14 patients. Follow-up MRI after a median of 3 months revealed 3 residual lesions corresponding to the large acute postablation lesions (>10 mm). The remaining 47 small or medium-sized lesions were not detectable at follow-up evaluation.

Larger volumes of cerebral lesions have been associated with cognitive decline and are uncommon findings acutely in post-ablation AF patients. Whether larger MRI-detected lesions represent the effect of solid thrombotic embolism and smaller lesions the endpoint of gaseous embolic events remains speculative. Most lesions heal in the short-term and although LA ablation is associated with small or medium-size SCI events, AF-ablation may prevent development of additional larger lesions occurring during the natural course of the AF disease. Of note, an apparent reduction in the risk of additional brain lesions was documented on follow-up MRI after AF-ablation.[35,59,69] Using a large database, Noseworthy, et al. recently evaluated 'real world' stroke rates in AF patients who underwent catheter ablation or cardioversion.[70] Among 24,244 patients, included in this propensity-matched analysis, the authors found that ablation is associated with a significant higher initial risk of stroke/TIA within the first 30 days (RR 1.53; p=0.05). However, over longer-term follow-up, ablation is associated with a slightly lower rate of non-TIA stroke (RR 0.78; p=0.03). Beyond symptomatic relief, AF ablation may provide

additional benefits;[71-74] although speculative, it is intriguing to propose that AF ablation may reduce the likelihood or delay the onset of dementia over the long-term[69] and warrants further investigations.

Since silent cerebral events secondary to AF ablation are common but not associated with impaired cognitive function, we do not believe that follow-up cerebral MRI should be routinely performed after AF ablation. It is possible that decline in cognitive functions is multifactorial and not correlated to focal lesions only. Post-ablation MRIs can be however considered to assess the potential embolic risk of new ablation devices/technologies for LA ablations.

Conclusions

Appropriate management of AF-patients has been engaging clinicians for many years. Diffusion-weighted MRI has documented asymptomatic ischemic cerebral lesions after most invasive cardiac procedures, including AF ablation. Given the heightened risk of dementia in AF patients not undergoing ablation, the relationship between AF and SCI is an old issue but only larger volumes of cerebral lesions have been associated with cognitive decline. From a pathophysiological point of view, new ischemic lesions on MRI after AF ablation, should suggest worse neuropsychological outcome; however, the available data are discordant. Most silent MRI-detected lesions observed acutely after AF ablation procedures are small or medium-size events and the majority of acute lesions regress at medium-term follow-up.

AF patients continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function. In this way, successful AF ablation has the potential to reduce the risk of cerebrovascular events that may be considered as part of the natural course of AF.[70,75,76] Although the long-term implications of SCI remain unclear, it is conceivable that strategies to reduce the risk of SCI may be beneficial.

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