Cerebrovascular Complications Related to Atrial Fibrillation Ablation and Strategies for Periprocedural Stroke Prevention

Zoltan Csanadi, MD, PhD[a,b,c,*], Edina Nagy-Baló, MD[a,b,c], Stephan Danik, MD[b,c,d], Conor Barrett, MD[b,c,d], J. David Burkhardt, MD[b,c,e], Javier Sanchez[b,c,e], Pasquale Santangeli, MD[b,c,f], Francesco Santoro, MD[b,c,g], Q2 Q3 Luigi Di Biase, MD, PhD[b,c,e,g,h,i], Andrea Natale, MD[b,c,d,e,i]
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KEYWORDS

- Atrial fibrillation • Stroke • Silent cerebral ischemia
- Diffusion-weighted cerebral magnetic resonance imaging • Transcranial Doppler

KEY POINTS

- Manifest, clinical stroke related to ablation of atrial fibrillation occurs in about 1% of patients.
- Silent cerebral ischemia can be detected by diffusion-weighted magnetic resonance imaging (MRI) in as many as 50% of patients postablation.
- The long-term significance of these silent lesions is not yet known.
- Postablation diffusion-weighted MRI and intraprocedural transcranial Doppler recordings of cerebral microemboli can be used to compare the thrombogenic potential of different ablation techniques.
- A safe periprocedural strategy using novel oral anticoagulants needs to be determined.
- Prospective randomized trials are needed to establish the optimal postablation care of patients regarding long-term anticoagulation.

Q8 INTRODUCTION

Transcatheter treatment of atrial fibrillation (AF) is a complex intervention requiring the introduction of hardware into the left atrium (LA), energy applications over a large area of the LA endocardium, and prolonged instrumentation in the systemic circulation.[1] Q9 Furthermore, these procedures are

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[a] Department of Cardiology, University of Debrecen, 22 Móricz Zs, Debrecen H4032, Hungary; [b] Case Western Reserve University, Cleveland, OH, USA; [c] Interventional Electrophysiology, Scripps Clinic, San Diego, CA, USA; [d] Al-Sabah Arrhythmia Institute (AI), St. Luke's Hospital, NY, USA; [e] Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX, USA; [f] Clinical Cardiac Electrophysiology, University of Pennsylvania, Philadelphia, PA, USA; [g] Department of Cardiology, University of Foggia, Foggia, Italy; [h] Albert Einstein College of Medicine, Montefiore Hospital, Bronx, NY, USA; [i] Department of Biomedical Engineering, University of Texas, Austin, TX, USA
Q7
* Corresponding author.
E-mail address: drcsanadi@hotmail.com

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performed in patients who are at inherently increased risk of a thromboembolic complication, including stroke. It is therefore not surprising that cerebrovascular accidents have been among the most feared complications since the inception of AF ablation, evoking significant concern.

INCIDENCE OF CEREBROVASCULAR COMPLICATIONS RELATED TO AF ABLATION

Stroke and Transient Ischemic Attack

The first worldwide survey on catheter ablation for AF concluded that clinical stroke occurred in 0.28% and transient ischemic attack (TIA) in 0.66% of patients. The update of that survey, relating to AF ablations performed between 2003 and 2006, indicated similar rates of cerebrovascular complications (0.23% for stroke, 0.71% for TIA) despite an apparently more challenging patient population with a more enlarged LA and more persistent AF.[2] A meta-analysis based on the data of 6936 patients who underwent AF ablation by the end of 2006 found that stroke and TIA occurred in 0.3% and 0.2%, respectively.[3] Stroke incidences as high as 5%[4] and as low as 0%[5] have also been reported as single-center findings. Although the complication rates associated with any procedure, including AF ablation, generally decrease with increasing experience, this was not demonstrated in a high-volume center: while the overall complication rate decreased over a 10-year period from 11.1% to 1.6%, the incidence of stroke and TIA remained unchanged.[6] Thromboembolic events typically occur within 24 hours of the ablation procedure, with the high-risk period extending for 2 weeks thereafter.[7] Stroke is a significant cause of periprocedural death during AF ablation. An international survey on AF ablation in 162 centers reported details of 32 deaths in 32,569 patients. The fatal outcome was attributed to stroke in 5 (16%) of these 32 cases.[8] On the other hand, patients who survive a stroke associated with AF ablation often have a favorable long-term prognosis. During a mean 38-month follow-up of 26 patients who suffered AF ablation–related stroke in a high-volume center (2 patients died), complete long-term functional and neurocognitive recovery was documented in most patients, irrespective of the severity of the periprocedural stroke.[9]

Silent Cerebral Ischemia

It has recently been recognized that silent cerebral ischemia (SCI) can be demonstrated by diffusion-weighted cerebral magnetic resonance imaging (DW-MRI) in a much higher proportion of patients undergoing LA ablation than in those with manifest stroke.[10–17] Lickfett and colleagues[10] performed DW-MRI before and after a Lasso-guided pulmonary vein (PV) ostium isolation (PVI), and demonstrated new cerebral lesions in 2 (10%) of 20 patients without overt clinical symptoms. Similarly, an 11% incidence of SCI was reported from the same center in a larger population of 53 patients.[11] In a large-scale study[12] of 232 patients undergoing PVI with or without linear lesions and targeting of complex fractionated electrograms (CFE) with irrigated radiofrequency (RF) ablation, new silent brain lesions were found on DW-MRI in 33 patients (14%). These initial results were followed by several single-center studies[13–18] that reported widely variable results, including an incidence as high as 50% for a new SCI depending on the ablation and the MRI technology used (Table 1). A recent study examined the ability of a 3-T MRI scan to detect cerebral injury. Of 22 patients who had undergone PVI using cryoenergy, the incidence of SCI was 50% as opposed to 27% of 15 patients who had undergone PVI using RF energy.[17]

Clinical Relevance of SCI

The clinical significance of SCI after AF ablation is at present uncertain. Deneke and colleagues[18] repeated DW-MRI 2 to 56 weeks (median 12 weeks) after ablation in 14 patients in whom a total of 50 new-onset, clinically silent white matter lesions were identified within 48 hours after ablation. No lesion with a diameter smaller than 10 mm could be identified on the repeated MRI even as early as 2 weeks after the ablation, whereas 3 larger lesions (>10 mm) were still detected. Of note, all of these follow-up lesions demonstrated a reduction in size with no hemorrhagic component in any of them, despite the patients being on oral anticoagulation (OAC). The disappearance or shrinkage of these lesions, although reassuring to some extent, does not imply the full recovery of pathologic alterations in the brain. In an elegant canine model, typical lesions were demonstrated on DW-MRI and fluid-attenuated inversion recovery images after the injection of gaseous and particulate microemboli.[19] Clear evidence of ischemic injury, including severe endothelial proliferation, moderate glia cell activation, and mild perivascular lymphocytic infiltrate, was present on histopathologic examination of brain specimens, despite the resolution of most lesions on MRI by day 4 postembolism.

In the general population of patients with AF, a high prevalence of SCI has consistently been detected on DW-MRI. These subclinical lesions were linked to an unfavorable long-term clinical

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Table 1
Silent cerebral ischemia detected by DW-MRI in various studies

Authors,[Ref.] Year	ACT	N	Ablation Technique	Positive DW-MRI
Lickfett et al,[10] 2006	>250	10	Irrigated RF ablation	1 (10%)
Schwarz et al,[13] 2010	>300	13	Irrigated RF ablation	3 (14.3%)
		9		
Neumann et al,[14] 2011	>300	44	Irrigated RF	3 (6.8%)
		45	Cryoballoon	4 (8.9%)
Gaita et al,[12] 2010	250–300	232	Irrigated RF ablation	33 (14%)
Schrickel et al,[11] 2010	>250	53	Irrigated RF ablation	6 (11%)
Herrera Siklódy et al,[15] 2011	>300	27	RF	2 (7.4%)
		23	Cryoballoon	1 (4.3%)
		24	Phased RF	8 (33%)
Gaita et al,[16] 2011	>300	36	Irrigated RF ablation	3 (8.3%)
		36	Phased RF	14 (38.9%)
		36	Cryoballoon	2 (5.6%)

Abbreviations: ACT, activated clotting time; DW-MRI, diffusion-weighted cerebral magnetic resonance imaging; RF, radiofrequency.

outcome, including an impaired cognitive function, an increased risk of dementia, and a worse prognosis of AF-related strokes in comparison with those of non-AF etiology.[20,21] A recent cross-sectional study of 180 patients with variable forms of AF demonstrated an 82% (paroxysmal) and a 92% (persistent AF) prevalence of SCI on MRI; the number of lesions per person was significantly higher in the patients with persistent AF than in those with paroxysmal AF.[22] Furthermore, the performance in cognitive function tests was significantly poorer in AF patients compared with matched controls.

However, these observations indicating the clinical significance of spontaneous ischemic lesions in AF patients may not be extrapolated to SCI induced by AF ablation. Whereas postablation SCIs are attributed to microembolization during or shortly after the procedure, the mechanism in patients with AF of variable duration is likely to be multifactorial, with the potential importance of both progressive atherosclerosis and showers of microemboli from the LA. Limited data are available on the cognitive function after AF ablation. Schwarz and colleagues[13] compared the results of neurophysiologic tests before and 3 months after PVI in 21 patients and found a poorer neurophysiologic outcome in verbal memory, but no difference in the other 4 cognitive domains evaluated (attention, verbal fluency, executive functioning, and visual memory). A battery of 8 neuropsychological tests was performed in a recent study on 150 patients, including 90 undergoing wide encircling antrum ablation for paroxysmal (60 patients) or persistent (25 patients) AF, 30 patients undergoing ablation for supraventricular tachycardia (SVT), and 30 patients scheduled for ablation of AF as a matched nonoperative control group.[23] The results at 90 days after ablation indicated postoperative cognitive dysfunction in 13% of the paroxysmal AF patents, 20% of the persistent AF patients, 3% of the SVT patients, and none in the control group. The only predictor of negative changes was the LA access time. The clinical significance of the subtle changes suggested by these data warrants further exploration.

Although direct evidence is still lacking, it is reasonable to assume that SCI lesions detected by DW-MRI are indicators of the thromboembolic consequences related to AF ablation; a preventive measure that successfully limits the subclinical event rate will also reduce the risk of manifest stroke. Its relatively high incidence therefore makes SCI a logical and practical surrogate of clinically overt cerebrovascular events in future clinical studies.

MECHANISM OF PERIPROCEDURAL THROMBOEMBOLIZATION

The postulated mechanisms of AF ablation–related cerebral embolization include embolism of particulate debris, thrombus, char, or gas bubbles at the site of the ablation in the LA.

Particulate Debris

Transseptal puncture may produce particulate debris in 2 different ways:

1. While advancing, the transseptal needle scrapes plastic particles off the inner wall of

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the transseptal dilator, thereby creating embolic material.[24]

2. The coring of cardiac tissue into the tip of the open-ended needle creates a small plug of cardiac tissue regardless of the puncture site and the type of the needle, including RF.[25]

Thrombus

The generation of thrombi relies on Virchow's triad: endothelial injury, hemodynamic changes (stasis and turbulence), and a hypercoagulable state.

Energy application during ablation injures endothelial cells. When the continuity of the endothelium is interrupted, its natural anticoagulation properties are lost and blood components come into direct contact with subendothelial procoagulant proteins, such as collagen, tissue factor, and von Willebrand factor. Consequently, thrombus formation is initiated through platelet adhesion and activation, and thrombin production.[26] Thrombi adherent to the endothelium may dislodge spontaneously or as a result of catheter manipulation, mechanical trauma resulting from electric cardioversion, and restoration of atrial contractility in sinus rhythm.[12] Of importance is that the thrombogenic potential is related to the energy applied: cryoablation has been shown to be less thrombogenic than RF.[27] The difference is explained by the histologic characteristics of RF lesions and cryolesions. Whereas those produced by the latter are well circumscribed with sharp borders, with sparing of most of the endothelial lining, RF lesions are characterized by intralesional hemorrhage and ragged edges, with a marked endothelial injury. Similarly to RF, all energy sources that ablate through heating, such as the microwave and the laser, carry an increased risk of thrombus formation.[26]

Energy delivery can also lead to embolization through the direct embolization of small myocardial fragments generated by steam-pops. This event is more likely to occur when the tissue is overheated because of the high contact forces and/or the high energy delivered during the ablation.[28] Char formation at the tip of the catheter in these situations is not uncommon, and may also be a potential source of embolization.[29]

Hemodynamic changes, including stasis and turbulence, may also contribute to thrombus formation during LA ablation. Stasis can occur in the transseptal sheath and in the trapped blood column in the PV behind an occluding cryoballoon, providing the proper milieu for thrombus formation, which may enter the systemic circulation during catheter exchange or deflation of the balloon.[12,30] The turbulent blood flow created by the catheter manipulation or the rapid injection of contrast material may induce a response that results in platelet activation, which in turn may begin the process ultimately leading to embolization.[31]

A hypercoagulable state develops during PVI through 2 main mechanisms. Heating of the circulating blood elements during RF energy delivery has been demonstrated to activate platelets and the clotting system.[32] However, the introduction of the catheters and sheaths themselves activates the coagulation cascade and induces a prothrombotic state.[33] This concept was demonstrated by Ren and colleagues,[34] who detected fresh thrombi attached to a sheath or mapping catheter by intracardiac echocardiography (ICE) in as many as 10% of the cases.

Gas Bubbles

As transseptal sheaths may potentially connect the LA with the room air, flushing through these sheaths, or introducing or exchanging catheters and guide wires, pose the risk of air embolization, even with the protection of hemostatic valves. The risk of air embolization is higher when catheters with a complex configuration are used.[35] Furthermore, gas embolization can occur during other phases of these procedures, including the energy delivery period, PV angiography, and catheter manipulation.[36] Microcavitation visualized as bubbles by ICE occurs during RF delivery, especially when the tissue temperature exceeds 60°C.[37] The phenomenon of cavitation, well known in stainless-steel turbines, dam outlets, and ship propellers, and first described in a cardiovascular context in connection with mechanical heart valves, involves the rapid formation of vaporous microbubbles in a fluid owing to a local reduction of pressure to below the vapor pressure.[38]

INTRAPROCEDURAL ASSESSMENT OF THROMBOEMBOLIC RISK DURING LA ABLATION

DW-MRI has become the gold standard for assessment of cerebral ischemia, either symptomatic or asymptomatic, after ablation. A real-time assessment of the thromboembolic risk during the ablation may improve the safety of the procedure. Two methods have been used for this purpose: the monitoring of microbubbles on ICE, and the detection of microembolic signals (MES) in the cerebral arteries by transcranial Doppler (TCD).

Monitoring of Bubble Formation by ICE During Ablation; Power Titration Strategy

ICE was originally introduced to interventional electrophysiology as a simple and reliable tool to display different cardiac structures and the positions of catheters in the heart,[39] to ensure safe transseptal puncture and the early recognition of complications during the procedure. ICE-detectable bubble formation during RF delivery was first described in an experimental model by Kalman and colleagues,[37] who noticed that showers of microbubbles often preceded an increase in impedance, indicating overheating of tissue during ablation. The concept was first tested in humans by Marrouche and colleagues,[40] who developed an energy titration strategy based on the microbubble density detected by ICE. Two types of bubble-generation patterns were defined: scattered microbubbles (type 1), indicating early tissue overheating, and a brisk shower of dense microbubbles (type 2) (Fig. 1). The energy was increased in stepwise fashion until the appearance of the type 1 pattern, and the power was then reduced. Energy delivery was immediately terminated in the event of the type 2 pattern. This strategy prevented any thromboembolic complication in 152 patients undergoing circular mapping–guided PVI, whereas stroke/TIA occurred in 3% of patients without ICE-guided power titration. Ablation of complex substrates including AF under ICE guidance with power titration has become a routine practice in many centers, although the assessment of bubble density is compromised by echogenic microbubble formation caused by the irrigation flow when open irrigated catheters are used. A semiquantitative scale describing the bubble density of 3 different patterns as few, moderate, or shower has also been used.

Fig. 1. Microbubbles detected by phased-array intracardiac echocardiography.

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Microembolic Signal Detection by Transcranial Doppler

Circulating cerebral emboli can be detected by TCD when imaging the middle cerebral arteries (Fig. 2). MES are characterized by short-term, high-intensity ultrasonic signals with characteristic audible chirps.[41,42] With older devices, the differentiation between true embolic signals and artifacts (probe dislocation or noise from external devices) requires an experienced observer. MES may be due to solid particles, or gaseous in nature. As there is a difference in their acoustic impedance, solid and gaseous emboli can be differentiated. The latter reflect the ultrasonic beam with a higher intensity than do denser particles. The use of novel multifrequency TCDs with imaging at 2 different frequencies (2 and 2.5 MHz) can automatically differentiate true signals from noise, and gaseous from solid emboli, thereby improving the practicality of the technique for routine clinical use.[43] Results of several studies have been reported with MES detection during cardiopulmonary bypass surgery and carotid interventions.[44] The clinical significance of these microemboli with regard to the postoperative neurologic state or the cognitive function of the patients is less well established.

Limited data are available on the number of MES during LA ablation for AF. Kilicaslan and colleagues[45] compared MES counts recorded during PV antrum isolation with ICE-guided power titration (as described earlier) versus that with conventional power-limited RF delivery in 202 patients. A good correlation was found between the intensity of bubble formation and the MES count. The power titration strategy resulted in half the total number of MES (mean = 1015) in comparison with the conventional approach (mean = 2250), and acute neurologic complications occurred in 0.9% and 3.1% of patients, respectively. Sauren and colleagues[46] reported a virtually negligible number of MES (mean = 5) during epicardial AF ablation in comparison with endocardial ablation (mean = 3908). In another study from the same group,[30] the MES counts detected during AF ablation demonstrated significant differences between 3 different techniques (cryoballoon, irrigated RF, and nonirrigated RF), in line with previous MRI results. Nagy-Baló and colleagues[36] recently reported on the results of intraoperative TCD and ICE recording in 34 patients undergoing PVI with either cryoballoon or phased-RF ablation. It is noteworthy that multifrequency TCD capable of

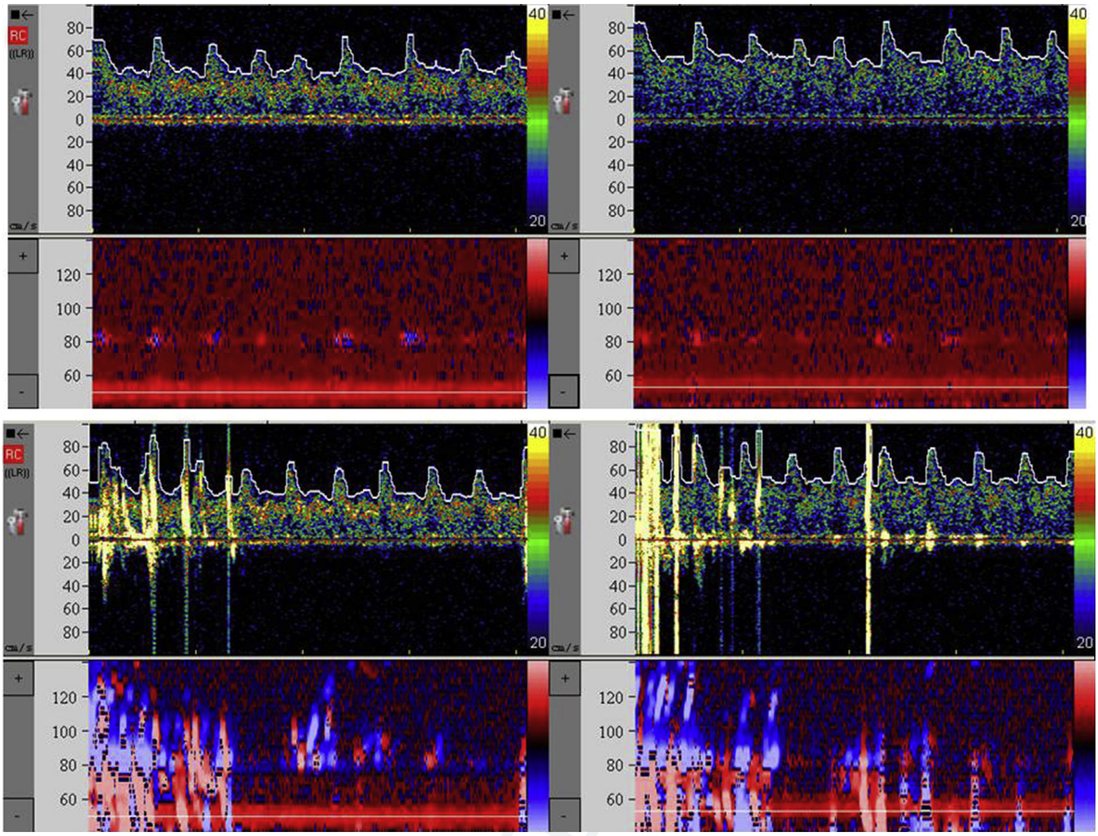

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Fig. 2. Bilateral transcranial Doppler recording of microembolic signals (MES) during radiofrequency ablation in the left atrium. MES can be observed on the lower but not on the upper panels.

automatic differentiation of gaseous and solid emboli was used to study the nature of the MES. A very significant correlation was demonstrated between the microbubble density and the MES count, confirming previous observations.[45] In line with published DW-MRI results, significantly lower total numbers of MES were detected during cryoballoon ablation in comparison with phased-RF ablation. This study was the first to investigate the nature of the MES, and demonstrated that 80% of them were of gaseous origin regardless of the ablation technique. The significance of the composition of the microemboli at this time is unclear. In theory, gaseous bubbles are expected to be less durable and less harmful than particles. With no data available on the relationship between the MES count recorded during ablation and postprocedural DW-MRI findings or manifest cerebral ischemia, it is not possible even to estimate the microembolic load that would indicate a significant risk of a symptomatic or an MRI-detectable lesion. However, MES detection promises to be a valuable tool to compare the thromboembolic potentials of different ablation techniques and strategies, and to gain further insight into the mechanisms of embolus formation relating to different stages of AF ablation.

CLINICAL AND ABLATION TECHNOLOGY–RELATED PREDICTORS OF CEREBRAL VASCULAR EVENTS

The risk of a periprocedural cerebral ischemic event, either symptomatic or subclinical, is influenced by multiple factors, including the baseline characteristics of patients and the technical aspects of the ablation procedure.

Patients' Characteristics

In a prospective multicenter study[47] on 6454 patients undergoing RF ablation for AF in 9 centers, stroke/TIA occurred in 27 patients (1.1%). Among the characteristics of the cohort, diabetes mellitus, congestive heart failure, and the type of AF (paroxysmal or nonparoxysmal) proved to be independent predictors of a periprocedural cerebrovascular event on multivariate analysis. In a single-center study,[48] 10 (1.4%) of 721 patients

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suffered a stroke/TIA during or within 30 days after AF ablation, and a CHADS2 score of 2 or higher and a history of previous stroke/TIA remained independent predictors of cerebral ischemia in 2 multivariate models.

Inconsistent DW-MRI results have been published regarding clinical predictors of SCI. In the largest population studied so far,[12] none of the clinical characteristics were predictive of SCI. Schrickel and colleagues[11] reported 6 new cases of SCI in 53 patients after focal RF ablation. Coronary artery disease; the number of failed antiarrhythmic drugs, an enlarged left ventricular volume, and septal-wall thickness were predictors of a positive DW-MRI finding. A Japanese study[49] found only left ventricular ejection fraction to be a positive predictor. In the MEDAFI trial,[14] which compared cryoablation and irrigated RF ablation (nonrandomized) in 89 patients, age was the only predictor of SCI.

Technical Aspects of the Ablation Procedure

Besides the ablation technology, consideration must also be given to the manipulation of the sheaths placed in the LA, and the types of energy and catheter used for the ablation.

Long sheaths, including those used to establish LA access during transseptal puncture and steerable sheaths designed to facilitate maneuvering in the LA, pose well-known hazards of air embolism during injections or flushing through these devices, and also during catheter exchange, as removal of the catheter can create a vacuum inside the lumen. These devices, mostly at their distal segment, are a source of thrombus formation, especially in the absence of appropriate and timely anticoagulation (**Fig. 3**). Continuous flushing of these sheaths and meticulous care to eliminate air bubbles are essential for procedure safety.[50] Furthermore, any catheter removal should be performed slowly with continuous suction on the side arm of the sheaths, followed by careful flushing. It is a common practice in many centers to keep the sheaths in the right atrium once the diagnostic and ablation catheters have been placed in the LA, thereby mitigating the risk and consequences of thrombus formation on the tip of the sheath. Besides other advantages, the routine use of ICE offers an opportunity for the continuous monitoring of all catheters placed in the heart, with the recognition of thrombus formation on them.[34]

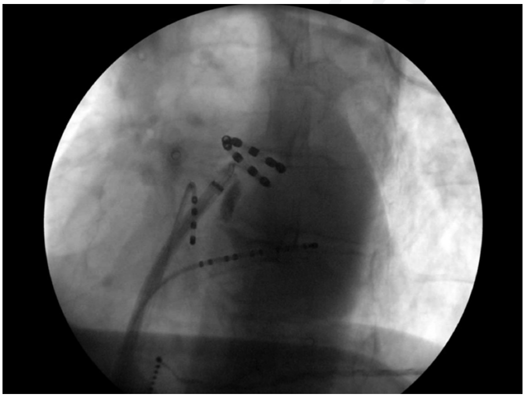

Fig. 3. Thrombus formation on the tip of a steerable sheath in the left atrium. Thrombus attached to the tip of the sheath is visible on fluoroscopy after contrast injection.

The ablation technology, including the type of energy and the catheter used for AF ablation, can lead to different risks. Since the early days of AF ablation, when RF energy was used exclusively with conventional 4-mm and then 8-mm tip ablation catheters, alternative energy sources including cryoenergy and laser have been introduced. In the present era, irrigation RF catheters have become the standard, and balloon-based and multipolar ablation technologies are popular in many centers. It is reasonable to assume that significant differences in thromboembolic risk may be associated with these different technologies. However, conclusive evidence as to the advantage of one technology over another, measured as a difference in the rates of manifest stroke/TIA, is not yet available, largely because of the relatively low occurrence of clinically overt events.

The much higher incidence of SCI events offers a better opportunity for the comparison of these ablation methods. In fact, significant differences have been demonstrated in the rate of SCI. Gaita and colleagues[16] reported a striking ablation technology-dependent difference in the incidence of SCI detected by MRI. In a randomized comparison of 108 patients, phased-RF ablation with a pulmonary vein ablation catheter (PVAC) was associated with a significantly higher (38.9%) incidence of acute lesions than was observed with irrigated focal ablation (8.3%) or cryoablation (5.6%). In 74 patients, Herrera Siklódy and colleagues[15] found new ischemia on DW-MRI in 37.5% after PVAC ablation, compared with 7.4% and 4.3% after irrigated RF and cryoablation, respectively. In a recent report,[51] the use of phased-RF ablation with a new generator and modified software to control power handling during RF applications decreased the incidence of positive findings on DW-MRI to 27%. Another publication by the same group[52] indicated that simultaneous RF delivery to no more than 2 electrode pairs and exclusion of the first and the last poles from the simultaneous energy application further reduced the incidence of SCI to 11.7%, at the price of a prolonged procedure time.

Although it seems reasonable to assume that the procedure (and/or the LA) time and the amount of ablation with the addition of lines or atrial defragmentation may also influence the thromboembolic risk, this has not been confirmed.[12,49] However, coronary angiography performed together with AF ablation[49] and cardioversion (either pharmacologic or electrical) during ablation[12] have been found to be positive predictors.

The available data on the number of MES detected by TCD during AF ablation also demonstrate marked technology-dependent differences (Table 2). Sauren and colleagues[30] observed significantly more MES during ablation with nonirrigated RF (mean = 3908) compared with irrigated RF (1404) and cryoablation (935). In a recent study, Nagy-Baló and coleagues[36] compared the number of MES during cryoablation and PVAC ablation using lower (≥250) and higher (≥320) minimum intraprocedural activated clotting time (ACT) target levels for PVAC. Irrespective of the level of anticoagulation, ablation with the PVAC (means = 3143 and 2205) resulted in significantly higher MES counts in comparison with cryoablation (mean = 834).

PERIPROCEDURAL THROMBOEMBOLISM PROPHYLAXIS AND LONG-TERM ANTICOAGULATION AFTER AF ABLATION

Thromboembolism Prophylaxis Before Ablation

Many patients undergoing AF ablation are at an elevated risk of a thromboembolic complication, and therefore require oral anticoagulation with a vitamin K antagonist (VKA) or a novel oral anticoagulant (NOAC) according to recent guidelines.[53,54] The 2012 expert consensus statement specified that all patients who have been in AF for 48 hours or longer or for an unknown duration need effective anticoagulation for at least 3 weeks before the procedure, or should undergo transesophageal echocardiography (TEE) to exclude LA thrombus.[50] The common practice in the past was bridging. The VKA was discontinued and changed to low molecular weight heparin (LMWH) a few days before the procedure, then switched back afterward. Performing AF ablation on a therapeutic level of anticoagulation (international normalized ratio [INR] 2–3.5) has recently evolved as the preferred approach in many centers, after several studies demonstrated its safety.[55,56] In fact, the risk of both thromboembolism and bleeding was reduced. With the recent introduction and rapid adoption of NOACs for thromboembolism prophylaxis in AF patients, a new strategy for the perioperative management of these patients is urgently needed. Comparison of uninterrupted warfarin and the direct thrombin inhibitor dabigatran, based on data from a multicenter prospective registry,[57] indicated significantly higher rates of major bleeding and the composite of bleeding and thromboembolic complications (6% and 16%) with dabigatran in comparison with warfarin (1% and 6%). All patients with thromboembolic complications who were on dabigatran had nonparoxysmal AF and more extensive LA ablation. It should be noted that dabigatran was suspended at least 12 hours (mean 16 hours) before the procedure, and was restarted within 3 hours after hemostasis. In another study,[58] dabigatran was used in 123 patients with paroxysmal AF with no bleeding or

Table 2
Microembolic signals detected by transcranial Doppler in different studies

Authors,[Ref.] Year	ACT	N	Ablation Technique	MES
Kilicaslan et al,[45] 2006	350–400	202	RF	1793 ± 547
Sauren et al,[30] 2009	>350	10	RF	3908 ± 2816
	200–250	10	Irrigated RF	1404 ± 981
	>350	10	Cryoballoon	935 ± 463
				P<.05
Sauren et al,[46] 2009	—	10	Epicardial RF ablation	5 ± 6
	>350	10	Endocardial RF	3908 ± 2816
				P<.0001
Nagy-Baló et al,[36] 2013	>250	10	Cryoballoon	834 ± 727
	>250	12	PVAC	3142 ± 1736
	>320	13	PVAC	2204 ± 1078

Abbreviations: MES, microembolic signal; PVAC, pulmonary vein ablation catheter.

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thromboembolic complications. However, in this study dabigatran was discontinued 5 days before ablation, a lower intraprocedural ACT target was set, and LMWH was started immediately after the procedure, with dabigatran being resumed 22 hours later. Dabigatran is known to intensify the effect of unfractionated heparin (UFH) on the activated partial thromboplastin time in vitro. As UFH is administered during ablation, this drug-drug interaction may increase the bleeding risk unless dabigatran is withdrawn at least 1 to 2 days in advance. Therefore, starting dabigatran 3 hours after the procedure, with another 2 to 3 hours required for it to reach its full anticoagulation effect, results in an unprotected time window of 5 to 6 hours during the early postablation period unless LMWH is used for bridging.

One study[59] examined the use of interrupted rivaroxaban (n = 321) in comparison with warfarin (n = 321) for patients undergoing PVI. Fifty-one percent of patients in both groups had paroxysmal AF. The respective rates of major bleeding (1.6% vs 1.9%) and embolic events (0.3% vs 0.3%) were not significantly different between those on rivaroxaban and those on warfarin. Further studies using rivaroxaban, as well as other NOACs (apixaban), will be needed to determine whether these agents offer a safer alternative for periprocedural anticoagulation without the need for bridging.

Preablation Exclusion of LA Thrombus

The presence of a thrombus in the LA should be excluded before ablation in all patients unless adequate anticoagulation is documented for at least 3 weeks before the procedure. However, it is the routine in many centers for all patients to undergo an evaluation shortly before the ablation, regardless of the presenting rhythm and previous anticoagulation. The gold-standard method is TEE. Multidetector computed cardiac tomography (CCT) has also been proposed to assess the LA appendage for thrombus, but good sensitivity was associated with poor specificity in several reports.[60] In recent publications,[61,62] further assessment with delayed CCT at 1 or 3 minutes improved the specificity and positive predictive value to 100%. In many centers, CCT is part of the routine preprocedure; because the CCT data are used for image integration with the electroanatomic mapping system, patient discomfort and the additional costs related to the TEE could be avoided by extending its use to exclude a preexisting thrombus. ICE has also been advocated as a supplementary tool to assess LA thrombus in the event of an equivocal TEE finding.[63]

Intraprocedural Heparin Administration

Intraprocedural anticoagulation involves UFH administered as an intravenous bolus followed by continuous infusion to maintain a target ACT. As thrombus can build up on the transseptal sheath within a very short time, after or even before crossing the septum, it has become a common practice to give the bolus before or immediately after the transseptal puncture.[64] The recommended ACT target is 300 to 400 seconds; some centers aim at a level of more than 350 seconds. The target ACT should be reached before the first energy delivery, and then checked regularly (every 20–30 minutes) throughout the procedure. Extra boluses of UFH should be given if the ACT level drops below the target value. UFH administration is discontinued once all catheters and sheaths have been withdrawn from the LA; sheaths from the groin can be removed at an ACT level lower than 200 seconds. Heparin is reversed with protamine in some centers at the end of the procedure.

Postablation Anticoagulation

Both theoretical considerations and clinical observations recommend oral anticoagulation for at least 2 months for all patients after AF ablation. A variable degree of atrial stunning, similar to that occurring with direct-current cardioversion, is present after AF ablation. Moreover, the fresh endothelial damage resulting from energy application in the LA itself is thrombogenic. It has been demonstrated that most post–AF ablation strokes occur within 2 weeks after the procedure.[7] In patients undergoing the ablation with therapeutic INR, VKA should be continued for at least 2 months according to current recommendations.[50] In those managed with the bridging strategy, LMWH should be restarted after sheath removal and continued until the therapeutic INR is reached. Alternatively, oral anticoagulation can be followed by an NOAC.

With no evidence from large-scale randomized trials regarding the long-term thromboembolic risk in these patients, the same therapeutic principles as in patients without ablation are to be applied. The decision should therefore be based on the CHADS2 or CHADS2-VASC score,[53,54,65] and not on the presence or type of AF after ablation. The prognostic value of these scores after ablation has recently been demonstrated.[66] The available, but as yet insufficient, data suggest that successful AF ablation does reduce the stroke risk, and that long-term antithrombotic prophylaxis may not be required in all patients. In a nonrandomized study 755 patients were followed for a mean of 25 months postablation. Late thromboembolic events were noted in 2 of 755 patients

(0.3%), both of whom were on OAC.[7] No cerebral complication occurred in 180 patients who had at least 1 risk factor for stroke, remained in sinus rhythm, and in whom anticoagulant therapy was stopped a median of 5 months postablation. In a recent observational study[67] on 3344 patients who underwent AF ablation in 5 centers, OAC was discontinued and aspirin was prescribed, regardless of the CHADS2 score, in those who had no recurrence of an atrial tachyarrhythmia or a severe LA mechanical dysfunction. In those with a CHADS2 score of 1 or more, anticoagulation was restarted in the event of recurrence of atrial arrhythmia. In 347 patients with a CHADS2 score of greater than 2, no thromboembolic events were observed during a mean follow-up of 28 months. Bleeding complications were significantly more frequent among those on chronic anticoagulant therapy.

SUMMARY

While improvements have been made to limit the incidence of thromboembolic events, especially stroke, during catheter ablation of AF, the optimal strategy to minimize such complications has yet to be determined. Although operator experience certainly plays a role in limiting the incidence of stroke, periprocedural anticoagulation strategies that minimize both bleeding and stroke in a standardized fashion have yet to be universally agreed upon. It is hoped that larger trials can be undertaken to definitively address these important concerns.

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