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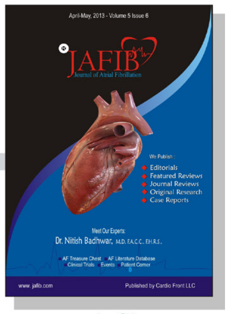

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Cerebral Embolization During AF Ablation – Pathophysiology, Prevention and Management

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Abstract

Catheter based ablation therapy has evolved as an invaluable tool in the management of symptomatic patients with atrial fibrillation (AF). The procedure of AF ablation requires instrumentation in the systemic circulation predisposing to various concerns that can result in systemic embolization. We will describe the reported incidence of these events and refer to the various pathophysiologic explanations for their occurrence. Details on the risk factors and the relevant studies will also be reviewed. Preventive and treatment strategies in patients undergoing the ablation procedure will be discussed.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia characterized by uncoordinated atrial activity resulting in thrombus formation in the atrium and the atrial appendage. AF is associated with substantial morbidity and mortality resulting from the embolization of the formed thrombus.[1] In the recent years there has been increasing identification of cerebral embolization in patients undergoing AF ablation. In addition to clinical events of cerebral embolism, there are other cases of asymptomatic embolization which can be recognized on imaging studies.[2] Though these are referred to as "silent emboli", multiple small emboli are associated with dementia as occurs in patients with persistent AF.[3,4] MRI has been established as a modality to identify infarcts in patients undergoing invasive procedures.[5] With the recent improved recognition of clinical and non-clinical cerebral embolism by imaging studies,[2] there have been several studies to evaluate this complication associated with ablation therapy.

Incidence

The reported incidence of thrombo-embolism associated with AF ablation is dependent on several factors including the investigation done to identify the cerebral embolism and duration of follow-up. In a large study of 589 patients undergoing circumferential pulmonary vein ablation for rhythm control, the incidence of clinical episodes of transient ischemic attack (TIA) and ischemic stroke was 8% and 4% during the 860 days follow-up.[6] There are no details of the timing of the events described. In another study of 755 consecutive patients using similar clinical signs to diagnose adverse events, the noted incidence of thromboembolic events was 0.9% within 2 weeks of ablation.[7] Two other studies including 79 patients and 211 patients undergoing RF ablation for symptomatic AF, report incidence of 2% within 24 hours and 1% in the early post procedural period.[8,9] In a worldwide survey on safety of ablation therapy for AF, the reported events of symptomatic stroke and TIA events were 0.23% and 0.71% respectively.[10]

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In a study by Gaita et al., 232 patients undergoing RF ablation for AF were evaluated with MRI scan pre and post procedurally to document the incidence of symptomatic and asymptomatic cerebral embolic episodes. Symptomatic cerebro-vascular accident occurred in 1 patient (0.4%) while cerebral magnetic resonance imaging was positive for new embolic lesions in 33 patients (14%).[11] In addition to the recognized clinical and non-clinical events of cerebral embolism, it is noted that thrombus frequently forms on the mapping and ablation catheter during the procedure. In a study of 232 patients undergoing LA RF ablation for AF, the incidence of LA thrombus was 10.3% during the procedure.[12] 57% of such thrombi were located on transseptal sheath and 43% being related to the circumferential mapping. The thrombus was recognized on intracardiac echocardiography images.

Patho-Physiology

The procedure of AF ablation requires introduction of catheter and sheath into the systemic circulation and the ablation lesions resulting in endothelial dysfunction predisposes to various concerns that can result in systemic embolization. The recognized underlying causes include thrombus formation on the catheters and guide sheaths, dislodgement of existing thrombus in the atrium, char formation on the catheter tip, denudation of endothelium by ablation, and microbubble air embolisation.[12,13,14,15,16]

It is recognized that manipulation of catheters even during diagnostic part of electrophysiological study is associated with increase in D-dimer levels, a marker of thrombogenesis.[13,14] In a study to assess the occurrence of thrombus formation during AF ablation therapy, there was noted high incidence of thrombus commonly attached to the transeptal sheath and the circular mapping catheter despite anticoagulation with heparin.[12] In a study by Dorbala et al., there were noted elevated levels of thrombotic factors thrombin-antithrombin complex (TAT) and prothrombin activation peptide and D-dimer levels in patients undergoing EPS procedure without ablation.[15]

In addition, ablation lesions result in disruption of the endothelial function and continuity in the atrium. In a study to assess endothelial damage marker (vWf) and tissue factor levels after RF catheter isolation of pulmonary veins, there was noted persistent elevation of the prothrombotic factors for 24 hours after ablation therapy.[16] The disrupted endothelial cells will also result in prothrombotic states as demonstrated by increase in D-dimer levels and thrombin-antithrombin III levels.[13,14] Though RF ablation was associated with elevation markers of thromboembolism, the concentrations were not observed to increase after RF ablation as compared with pre-ablation levels, suggesting that thrombin is generated more in response to catheter manipulation than radiofrequency energy delivery.[13,14,15]

Formation of coagulum over the ablation catheters may also result in embolization to the cerebral circulation.[17] Thrombi can form on the catheters during invasive procedure which can embolise. Any intra-procedural introduction of catheters or sheets in the left atrium can result in air microbubbles.[17,18,19] These air bubbles can be introduced during intra-procedure aspiration, irrigation or sheath/catheter exchanges. In a study of transcranial Doppler, there were noted air emboli in the carotid arteries during RF ablation procedure.[20] Conversion to sinus rhythm in patients with persistent AF after ablation therapy may also be a predisposing factor. Restoration of sinus rhythm by LA ablation results in return of LA function in patients in patients with chronic AF [21] which in-turn can result in dislodgement and embolisation of unrecognised atrial thrombus.

Risk factors

Risk factors for thromboembolism in patients with AF are well established ($CHADS_2$ and CHA_2DS_2-VASc).[22,23] These factors have been also evaluated for predicting thromboembolism in patients undergoing ablation therapy. In a study by Choi et al.,[24] the $CHADS_2$ and CHA_2DS_2-VASc scores were used to predict events in 565 patients with AF who underwent catheter ablation. The clinical endpoints of thromboembolic event or death occurred in 4.8% patients during 40 months follow-up. The $CHADS_2$ and CHA_2DS_2-VASc scores were independent predictors of adverse events in separate multivariate models. It was noted that patients with $CHADS_2$ score ≥2 had significantly higher events than patients with risk score of <2. There was no difference between $CHADS_2$ and CHA_2DS_2-VASc scores in predicting events. As regards to the independent factors, age, congestive heart failure, hypertension, prior stroke/TIA were associated with events while gender and diabetes mellitus were not. Though no specification on the timing of the adverse events was reported, it appears that most events occurred months after the ablation therapy. A very different finding was noted in a study to assess the occurrence of intra-cardiac thrombus formation during AF ablation. In this study of 232 patients undergoing pulmonary vein ostial ablation, the occurrence of intra-cardiac thrombus as identified by intracardiac echocardiography, none of these factors (age, gender, heart disease, and history of prior embolic event) were associated with thrombus formation.[12] LA diameter, spontaneous echo contrast and history of persistent AF were associated with left atrial thrombus formation on univariate analysis.[12] On multivariate analysis only spontaneous echo contrast was associated with LA thrombus. In another trial of 232 consecutive patients with paroxysmal or persistent AF who were candidates for RF ablation, none of the clinical parameters such as age, hypertension, diabetes mellitus, previous history of stroke, type of atrial fibrillation, and preablation antithrombotic treatment showed significant correlation with ischemic cerebral embolism.[11] The anticoagulation level during the procedure as assessed by ACT value, correlated significantly with the incidence of cerebral embolism. Amongst patients with ACT < 250 seconds, 17% had positive MRI, whereas for those with ACT value >250 seconds, 9% of the patients were positive for silent embolism. Intraprocedural cardioversion represents a pertinent risk factor with a significantly increased odds ratio of 2.75. In a study to determine if the intensity of anticoagulation reduces LA thrombus formation as detected by ICE during RF ablation in patients with spontaneous echo contrast, the incidence of LA thrombus was 45% in patients with activated clotting time 250-300 seconds and 5% in patients with ACT of more than 300 seconds.[25] In patients with and without SEC, keeping ACT above 300 reduced LA thrombus incidence from 11% to 3%. Total procedure time and time to heparin administration have been associated with the levels of vWf and DD concentrations (endothelial markers of thrombosis) after RF ablation in 30 patients underoing pulmonary vein isolation procedure.[16] In a study comparing cryoablation with RF ablation for management of AF, the incidence of MRI detected cerebral embolism was 7.9% within 1 day after pulmonary vein isolation, without statistically significant difference between the group treated by cryoenergy (8.9%) and radiofrequency ablation (6.8%).[26] In an observational study of 74 patients undergoing ablation therapy for AF, the incidence of cerebral infarcts was significantly higher in patients in the pulmonary vein radiofrequency ablation non-irrigated catheters when compared to irrigated RF and cryoballoon ablation.[27] In this study 27 patients underwent irrigation RF ablation while 24 patients underwent cryoballoon ablation. 24 patients underwent non-irrigation RF ablation with a circular mapping and ablation system capable of duty-cycled phased unipolar and bipolar RF delivery. On imaging with MRI on all patients, 7.4% of irrigated RF patients, 4.3% of cryoballoon patients, and 37.5% of non-irrigated circular mapping and ablation patients had new embolic events (p=0.003). A similar finding of silent cerebral thromboembolism was noted by Gaita et al.[28] In this study of 108 patients undergoing ablation therapy for paroxysmal AF, pulmonary vein ablation with multielectrode non-irrigated catheter increased the risk of thromboembolism by 1.5 times when compared to irrigated RF and cryoballoon ablation.

Prevention and Treatment

The approaches can be categorized into pre-, intra- and post-operative measures.

Pre-Operative

Identification of patients who are at a higher risk of thromboembolism needed to be informed of the risk. Though clinical risk factors including age, diabetes, hypertension, heart failure and prior history of stroke are associated with embolic events after ablation therapy, they appear to occur several months after the procedure and not in the immediate peri-procedureal period. Factors that need to be considered include LA diameter, presence of spontaneous echo contrast and presence of persistent AF at the time of ablation. Patients with persistent AF at the time of the procedure need to be screened with imaging study considering that catheter manipulation could dislodge a thrombus with the potential for embolic complications. Current guidelines recommend managing patients with AF at the time of the procedure to be the same as that for a cardioversion.[1]

Intra-Operative

A careful awareness to the anticoagulation throughout the procedure especially when the catheters are in the left atrium is critical. It is essential to understand that optimal anticoagulant should minimize the risk of thromboembolism and also bleeding risk. Keeping the ACT between 250 and 300 seconds is recommended by Venice Chart International Consensus during ablation procedure.[29] Patients with spontaneous echocontrast in the LA are at a higher risk of thrombus formation and may benefit with keeping the ACT >300 sec.[25] There has been no study to identify whether adding antiplatelet medications would reduce these events.

The routine practice of withholding warfarin and bridging with parenteral anticoagulation (unfractionated heparin and low molecular weight heparin) is associated with higher bleeding risk and has not been associated with reduction in embolic events. Several invasive cardiac procedures including pacemaker implantation requiring skin incisions and venous access can be safely be performend on warfarin without bridging with heparin.[30] Use of coumadin through the ablation procedure has been shown to be safe and also prevent stroke and TIAs.[31,32] There has been no noted increase in bleeding events with using warfarin in the peri-procedural period.

With the available newer anticoagulant agents, there have been studies to assess the use of Dabigatran on periprocedural embolism and bleeding. In a study by Lakkireddy et al., 145 patients with AF undergoing RF ablation therapy on dabigatran were compared with age, sex and type of AF matched 145 patients who were on uninterrupted warfarin at the time of undergoing AF ablation.[33] The dabigatran group consisted consecutive patients receiving dabigatran 150 mg twice daily for at least 30 days before the ablation procedure. The medication was held on the morning of the procedure and restarted at 3 hrs after obtaining hemostasis. UFH was given during the procedure to maintaine ACT between 300 and 400 sec when the catheter was in the left atrium. A 3.5-mm open irrigated tip RF catheter was used in all the patients. The use of dabigatran in the perioperative period was associated with similar thromboembolic events as warfarin (2.1% vs. 0%, p=0.25). Patients on Dabigatran had significantly higher events of major bleeding (6% vs. 1%; p = 0.019) and composite of bleeding and thromboembolic complications (16% vs. 6%; p=0.009) compared with the warfarin. All the major bleeds were in the form of pericardial hemorrhage requiring surgical drainage. On multivariate analysis, use of dabigatran and age more than 75 yrs were associated with bleeding risk. In another study by Winkle et al.[34] there were no increased events of bleeding or thromboembolic events with dabigatran. In this study 34 patients underwent periprocedural use of dabigatran. In this study dabigatran was stopped 36 hours before the procedure and restarted 22 hours after the procedure. Warfarin was stopped 5 days before the procedure and subcutaneous heparin was used until the procedure. Use of open irrigated ablation catheter, and pulling the sheaths back into the right atrium during ablation are associated with reduction in embolic events. Thrombus formed on the sheath or catheters are usually firmly attached and can be removed from the left atrium by withdrawing the sheath and catheter. In the study by Ren et al., 90% of the thrombus identified by ICE during ablation procedure could be eliminated by withdrawing the sheath and catheter.[12] Use of intraoperative intravascular echocardiography will help in early identification of thrombus over the catheters and hence prevent embolic episodes.

In addition to the thrombus risk, every precaution to avoid development of air pockets in the sheath needs to be made. The sheaths need to be aspirated and flushed with heparinized saline. The sheaths need to be connected to continuous flush with heparinized saline. The above intra-procedural strategies have reduced the incidence of systemic thromboembolism from 5% to 6% to < 1% in the more recent literature.[10,31,35]

Post operative

After the ablation procedure, anticoagulation should be restarted after the access sheaths are removed. Heparine infusion should be titrated to keep the PTT between 60 and 80 seconds. Patients should be restarted on oral anticoagulation with warfarin and LMWH could be used as a bridge until the the international normalized ratio is > 2. Anticoagulation needs be continued in the post procedural period. Witholding anticoagulation puts the patients at higher risk considering that patients with persistent AF who have reverted to sinus rhythm can form thrombus in the atrium to cause systemic embolisation. $CHADS_2$ and CHA_2DS_2-VASc scores can be used in assessing the thromboembolic risks. Patients with $CHADS_2$ score of 2 or more are at high risk of cerebro-vascular events and need to be on anticoagulation.

Conclusions

LA catheter ablation is associated with substantial events of asymptomatic and symptomatic cerebral embolism. Variables associated with thromboembolic events in the periprocedural period include LA diameter, presence of spontaneous contrast in the left atrium, duration of ablation therapy, and anticoagulation levels during the procedure. Non-irrigated tip RF catheters are associated with significantly risk of cerebral embolism when compared to irrigated RF catheters and cryo-ablation. $CHADS_2$ and CHA_2DS_2-VASc scores are associated with long term risk of thromboembolism after ablation therapy and have not been helpful in predicting periprocedural risk. Appropriate anticoagulation, withdrawing the sheath and catheter from the LA will reduce the risk of thromboembolism.

Disclosures

No disclosures relevant to this article were made by the author.

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