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Collateral Damage During Ablation of Atrial Fibrillation – Lessons Learnt in the Past Decade

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Introduction

Atrial fibrillation (AF) is a common tachyarrhythmia. There are over 2 million patients in the US with AF currently,[1] and as the median age of the population increases, the prevalence of AF likely will as well. Strategies for treating AF are diverse, and include options ranging from simple observation to pharmacotherapy to catheter-based and surgical interventions. Therapeutic approaches to AF historically have been divided into rate-control and rhythm-control categories, the former focusing on simply reducing ventricular response rates and the latter on restoration of sinus rhythm.Over the last 15 years, there has been an explosion of rhythm-control therapies, particularly in the field of catheter-based ablation. The proliferation of these ablative approaches has led to new insights into AF, both in terms of the mechanism(s) of the disease itself, and in the potential harm that patients can suffer during attempts at restoration of sinus rhythm. This review focuses on the complications, both the familiar and the newly appreciated, that may occur during catheter ablation of AF.

Definition of Pericardial Fat

In the late 1950s, Gordon Moe hypothesized that AF was the consequence of multiple, wandering reentrant waves coursing through atrial tissue.[2,3] His hypothesis was confirmed by the work of Allessie and colleagues thirty years later,[4-6] when they demonstrated that sustained AF depended on functional reentry of multiple wavefronts through a critical mass of atrial tissue. At approximately the same time, Haisseguerre and colleagues demonstrated that initiation of AF was triggered by spontaneous ectopy originating from foci in the pulmonary veins(PV).[7] Thus, the mechanisms of AF – functional reentry dependent on a critical mass of atrial tissue, triggered by ectopic beats within the PVs – were partially understood. Those mechanisms (triggers and substrate) constitute the primary targets for modern AF ablation. Other aspects of AF induction and perpetuation, including the role of ganglionic plexi and stable rotors, have also been proposed as important physiological modifiers of AF and as ablation targets.[8]

As the mechanisms underlying AF were determined, strategies to treat AF with catheter ablation evolved accordingly. Early ablative procedures focused on disrupting the critical mass of atrial tissue thought to be critical for perpetuation of AF. Linear lesion sets in the right atrium, left atrium, or both were delivered with the goal of interrupting reentrant circuits.[9-12] These stragies, though, were of limited efficacy at eliminating AF. With the observation by Haisseguerre that AF was triggered by PV foci, ablative strategies targeting the PVs were adopted. Initially, focal abla-

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tion of the PV foci themselves was performed,[7,13,14] but focal ablation gave way to segmental[15] and eventually to circumferential lesions designed to isolate, rather than eliminate, PV targets.[16-19] Currently, most practitioners employ one or both of these approaches (segmental ablation and/or circumferential ablation), with the goal of isolating each of the pulmonary veins, either individually or with its ipsilateral companion vein. In certain patient populations (i.e. patients with persistent or longstanding persistent AF), some operators deliver additional lesion sets to further divide atrial tissue, eliminate rotors, or destroy ganglia.[8]

Changes in the ablation procedure itself have been mirrored by changes in technologies used to deliver ablative lesion sets. Early procedures were performed exclusively with radiofrequency (RF) ablation delivered with non-irrigated (initially) and then irrigated (most current practice) catheters. However, RF energy is now one of many options. Alternative energy sources, including cryoablation, microwaves, laser ablation, and focused ultrasound have come (and in some cases, gone).[20] Similarly, alternative methods for delivering that energy to atrial tissue, including lasso-shaped catheters and balloon-based technology (designed to deliver circumferential lesions to a PV through an occlusive balloon positioned at the ostia) are new methods available to operators now.

With the development of new ablation strategies, energy modalities, and delivery systems, there has been a parallel evolution in the harm done to patients during ablation of AF. New techniques, while potentially safer in some regards, have uncovered new risks as well.

PV Stenosis

One of the primary lessons learned by the AF ablation community over the last decade is to avoid excessive energy delivery in the body of the PVs themselves. Early, focal ablation procedures targeting PV foci per se required RF delivery deep in the veins. Not only was this focal strategy of limited efficacy (due both to recovery of the ablated tissue and to the emergence of other PV ectopic sites unrecognized at the time of the initial procedure), but resulted in prohibitively high rates of PV stenosis[21,22] and related complications including dyspnea, pulmonary hypertension, and even death.[23] Segmental ablation, which moved the lesion set from deep in the vein into arcing lesions around the PV ostia, reduced the rates of PV stenosis and associated complications. That rate has been reduced further by widespread employment of wide, circumferential lesions around ipsilateral PVs, reduced power delivery when ablating between ipsilateral veins, and the use of imaging technologies (electroanatomic mapping systems; intracardiac ultrasound; merging with CT or MRI images of the left atrium and PVs) to delineate the PV-atrial junctions. Natale and colleagues reported results nearly a decade ago that demonstrated the importance of these factors in a large case series.[24] Ablative strategies that intentionally targeted distal sites in the PVs resulted in severe PV stenosis rates of 20%, while strategies that targeted ostial sites with intracardiac ultrasound to guide lesion delivery resulted in severe stenosis in 1.4% of patients. When ultrasound was also used to guide power delivery, no severe PV cases were observed. Other centers have confirmed that lesion delivery close to the PV ostium increases the risk of severe stenosis, and that mild to moderate stenosis (PV diameter reductions on the order of 50%) are seen in nearly a third of patients. Whether this is true stenosis or salutary remodeling of the left atrium (including the PV ostium) is not yet clear.

New ablation technologies, including RF catheters capable of delivering segmental lesion sets (Pulmonary Vein Ablation Catheter, or PVAC) and catheters delivering cryoablation through an occlusive balloon approach, have not eliminated the potential for PV stenosis. A study of 100 patients undergoing PV isolation using the PVAC device evaluated PV anatomy with paired pre- and post-procedure MRI or CT imaging. The authors found that the incidence of severe PV stenosis was 0%, but that some stenosis was seen in 7% of the PVs assessed.[25] Unlike the PVAC device, which delivers RF energy and requires careful positioning by the operator to avoid poorly targeted lesion delivery deep in the vein, cryoablation devices are thought to cause less tissue injury and remodeling of the sort that can result in PV stenosis. Large early series investigating cyroballoon ablation for PV isolation have shown no incidents of PV stenosis.[26] However, PV stenosis has been reported using the cyroballoon, albeit at the case-report level.[27]

In summary, there is clear evidence that avoiding RF delivery in the body of the PVs, and carefully titrating power delivery near the PV ostia, is critical in reducing the risk of PV stenosis to acceptable levels. While alternative energy sources may reduce the risk of PV stenosis further, the risk remains nonetheless.

Phrenic Nerve Injury

Injury of either the right or left phrenic nerve, with attendant hemidiaphragmatic paralysis and dyspnea, is a reported complication of AF ablation. The rate of this complication with circumferential isolation of ipsilateral PVs using RF energy appears to be quite rare. In a series of 3755 patients undergoing AF ablation using a variety of strategies, the global incidence of phrenic injury was 0.48%.[28] Right-sided phrenic injury was seen with ablation around the inferoanterior aspect of the right superior PV and the posteroseptal SVC, and left phrenic injury was seen (more rarely) with ablation at the base of the left atrial appendage. In 66% of cases, the function of the phrenic nerve and diaphragm recovered within several months. While standard PV isolation using RF energy delivered circumferentially around the PV ostia has a low risk of phrenic nerve injury, the introduction of new ablation modalities has renewed operator appreciation for phrenic damage. Early studies of cyroballoon ablation showed high rates of phrenic injury, particularly during ablation of the right superior pulmonary vein. Neumann and colleagues reported that in a series of 346 patients undergoing cyroballoon ablation, 26 patients developed phrenic nerve palsy during ablation of the RSPV.[26] Nearly all of these patients underwent ablation using a small balloon (23mm), likely resulting in a deeper lesion set in the vein. All patients recovered phrenic function by 1y. Other series have reported similar rates of phrenic damage, even while using larger balloons and monitoring closely for phrenic function by pacing the nerve during freezing.[29] Standard practice now while using this catheter is to pace the phrenic nerve during lesion delivery to the RSPV, and to immediately cease freezing if there is compromise in diaphragmatic function. Similar strategies may be helpful while delivering RF energy to the SVC, in cases when extra-PV ectopic foci are targeted. While it appears that even with this strategy, some patients may suffer from phrenic palsy and diaphragmatic paralysis, it also appears that most patients recover diaphragmatic function after several months.

Esophageal Injury

The esophagus and the posterior wall of the left atrium are adjacent structures. One rare but devastating consequence of AF ablation is esophageal injury resulting in atrio-esophageal fistula. The results of this complication are frequently lethal, and were initially reported in the cardiothoracic surgical literature as a consequence of left atrial ablation. In 2004, several reports of catheter-based ablation procedures resulting in atrio-esophageal fistula were published, alerting electrophysiologists to the issue.[30, 31] Since those initial reports, a number of procedural modifications have helped to reduce the incidence of clinically manifest esophageal injury. These include temperature monitoring within the esophagus itself, as well as reduced power delivery to the posterior aspect of the left atrium. Using these safeguards, the rate of this highly morbid complication has remained low. A worldwide survey of ablation practitioners reported that the rate of atrioesophageal fistula was 0.04%.[32]

There may be a significantly higher incidence of subclinical esophageal injury that occurs in patients undergoing PVI, despite temperature monitoring and limited power delivery to the posterior LA. Several studies have demonstrated, using post-procedure endoscopy, that esophageal lesions are relatively common in patients undergoing PV isolation.[33, 34] This is true even when power delivery to the posterior LA is limited to 25W and esophageal temperature is monitored. Whether prophylactic use of proton pump inhibitors can effectively reduce esophageal injury is not clear, though many centers treat their patients presumptively.[35] In addition, injury to periesophageal structures has been shown after PV isolation, even in patients without apparent mucosal injury to the esophagus itself.[36] The clinical relevance of these silent lesions is not known at present.

In summary, there has been a new appreciation for the potential of esophageal injury and the formation of atrio-esophageal fistulae after PV isolation.

Limiting power delivery to the posterior LA wall and monitoring esophageal temperature appear to be important in limiting the occurrence of this devastating, frequently fatal complication.

Atrial Septal Defect

One of the requisite steps while performing PV isolation, independent of ablation strategy, energy modality, or catheter type used, is the need to deliver that catheter into the LA. This is typically achieved through transseptal puncture from the RA to LA. A number of techniques for this procedure have been described, including double transseptal puncture, single puncture with the advancement of two sheaths through that single puncture site, or single puncture with introduction of a system capable of electrogram monitoring and ablation/freezing. A number of investigators have performed routine imaging of the atrial septum following PV isolation, and have demonstrated the occurrence of iatrogenic atrial septal defects with left-to-right shunting.[37-39] ASD formation appears to be related to the size of the sheath(s) delivered across the puncture site. Double-transseptal puncture with 8Fr sheaths delivered individually into the LA did not result in iatrogenic ASDs, whereas a single transseptal puncture with two sheaths delivered through that site resulted in higher rates of ASD formation.[38] Similarly, large sheaths (of the sort used for cyroballoon ablation) have been shown to result in ASD formation.[37] Longitudinal studies of these same patients have shown, however, that the ASDs resolve after several months in the majority of patients. What clinical relevance temporary or lasting ASD formation has for patients is not clear.

Periprocedural Embolism and Stroke

One of the most feared complications of AF ablation is systemic thromboembolism and stroke. While AF ablation techniques and technologies have evolved over time, large single-center series have shown that stroke remains a persistent, albeit rare complication. A series of 1190 procedures performed between 2001 and 2010 at Johns Hopkins showed that rates of many particular complications have fallen over time, but that the rate of stroke has remained nearly constant over the same period (at just under 1%).[40] Predictors of stroke in the Hopkins series were CHADS score ≥ 2 and prior history of stroke. All patients in this series underwent bridging with heparin around the time of their procedure. Other large series have demonstrated similar rates of thromboembolism in patients undergoing catheter ablation using a heparin-bridging strategy, and have shown that adopting a strategy of continuous therapy with warfarin at the time of the procedure reduced thromboembolic events to 0% without appreciable increases in bleeding complications.[41] Strategies to reduce the risk of thromboembolism that appear to be widely accepted at present include the use of irrigated RF catheters for PV isolation, anticoagulation strategies that minimize interruption of systemic anticoagulation (with continuation of warfarin and supplemental therapy with heparin during the procedure now being performed routinely by many centers), and meticulous attention to catheter and sheath management during LA access.

A number of series have shown that clinically silent microembolism occurs with high frequency, even in patients without apparent cerebrovascular or other systemic embolic events. A report on 53 patients undergoing PVI using a heparin-bridging technique and irrigated RF catheters found that post-procedure MRI showed detectable cerebral embolic events in 11%.42 Other studies have compared the rate of silent microemboli in patients undergoing cyroballoon ablation versus standard RF ablation, with all patients undergoing heparin bridging. Cerebral microemboli were seen in nearly 8% of patients on follow-up MRI scans, with no difference between cyroballoon and RF patients.[43] The clinical significance of these lesions is unclear.In summary, stroke remains a persistent, feared complication in patients undergoing PVI, despite the evolution of new ablation strategies and technologies. The use of irrigated catheters and anticoagulation strategies that minimize disruption of systemic anticoagulation (e.g. continuation of therapy with warfarin) appears to minimize stroke risk. Clinically silent microemboli likely occur in a significant minority of patients.

Specific Populations

One of the central questions in treating patients with symptomatic AF is whether to pursue rhythm control with anti-arrhythmic drug thera-

py aggressively, or whether to refer patients for ablative therapy early in the course of their disease. The CABANA trial, an ongoing, prospective randomized study comparing the effects of drug therapy versus first-line ablative therapy, will hopefully provide some answers to that question. Until then, operators must rely on a number of smaller series that report efficacy and complication rates in select populations.

Marchlinski and colleagues followed outcomes in a series of over 1500 patients undergoing ablation for AF, and divided the cohort by age (<45y, 45-54y, 55-64y, and >65y).[44] They found that across all age groups, there was a high rate of improved symptom burden (82-88% of patients, with no significant differences across age distribution). No major complications were seen in the youngest group, and complication rates increased slightly but significantly with age (2.6% major complication rate in patients >65y). The authors concluded that, because of the highly favorable risk-to-benefit ratio of ablation in the youngest cohort of patients, ablation is reasonable first-line therapy in those patients younger than 45y old.

Other studies have examined whether advanced age is an independent predictor of adverse outcomes in patients undergoing PV isolation. In a series of 1190 patients at Johns Hopkins, we found that age did not predict complications, although female gender and increased CHADS score did.40 Other centers have reported similar results. Marchlinski and colleagues examined patients stratified by age, and found comparable procedure efficacy and complication rates in patients >75y old versus patients in younger age brackets.[45] Natale and colleagues reported results from a series of 175 patients >75y old, and found that acute, major procedural complications occurred in 1% of patients.[46] They also found, though, that 3 other patients had a CVA within 6wks of the procedure, suggesting that there is a higher post-procedure morbidity rate (as one might expect) in the elderly. Whether gender plays a role in predicting complications during AF ablation is an unresolved question. At least two large series have found that female gender is an independent predictor [5]of major complications, even when controlling for age and other comorbidities.[40, 47] Other investigators have not found any clear correlation between gender and procedural outcomes (either efficacy or complication rates), however.

Cardiac Tamponade, Vascular Injury, and Other Complications

Mechanical injury to vascular or cardiac structures, resulting in pseudoaneurysm, groin hematoma, retroperitoneal hematoma, arterio-venous fistula, pericardial tamponade, or other trauma, are well known potential consequences of AF ablation. This reflects the necessary, aggressive instrumentation required to perform PV isolation. Typically 3, 4, or 5 large sheaths are advanced into the heart, 1 or 2 transseptal punctures are performed, and extensive manipulation and ablation is performed in the thin-walled left atrium, all in a setting of high-level anticoagulation. In 2005 Haissaguerre reported on a series of 348 patients undergoing PV isolation, with many patients also receiving linear ablation in the left or right atrium.[48] The incidence of tamponade in the PV isolation group was 1%; the incidence in patients receiving linear ablation in addition was 6%. Most of these lesions were due to steam pops, rather than mechanical perforation. Unfortunately, even with reduction of target power delivery midway through the series, the rates of steam pops and attendant injury and tamponade persisted.

Death from PV stenosis is fortunately quite rare. The largest investigation of procedurally related deaths surveyed 162 centers and collected results from 45,115 procedures performed between 1995 and 2006.49 The death rate was 0.98 per 1000 cases (32 total deaths), 8 of which were due to cardiac tamponade, 5 to stroke, and 5 to atrioesophageal fistula. Other causes were more rare, and included pneumonia (2), MI or arrhythmic death (2), sepsis (1), hemothorax (1), respiratory arrest (1), multiple PV occlusions (1), and other causes.[49]

Evolution of AF Ablation Over Time

Many of the large series reporting AF ablation efficacy and complications are confounded, necessarily, by evolving practice patterns and available equipment. Put another way, AF ablation has changed significantly over the past decade to become a safer and more effective procedure. This is likely a reflection of improved ablation strategies,

technological innovation, and a dissemination of information about newly appreciated complications (i.e. atrioesophageal fistula).

In a decade-long, single center experience at Johns Hopkins, we found that major complication rates have decreased significantly over time, from 11% early in the decade to 1.6% in 2010.[40] This reduction in complications was driven primarily by a fall in catheter-induced complications (i.e. perforation, phrenic injury, PV stenosis). Stroke rates remained consistent at nearly 1% across the decade.No deaths or atrioesophageal fistula cases were observed (though one case of esophageal injury using an experimental, focused ultrasound balloon catheter was seen). Other series in recent years have shown similarly low complication rates, due in part to careful patient selection and to the development of safer ablation strategies and technologies over the last ten years.[44, 50]

Conclusions

Catheter ablation for AF is a complex, technically challenging procedure. Despite advancements in ablative strategies, energy sources, and catheter systems – and indeed, in some cases because of those advancements – the potential to harm patients persists. Across various types of complications, there appear to run several truisms that correlate with reduced risk. These include limiting excessive power delivery to delicate structures (i.e. the posterior LA and esophagus, PV ostia and the veins themselves), maintaining constant vigilance during the procedure, and proactively monitoring for harm (i.e. pacing the phrenic nerve during certain ablations), and avoiding unnecessary interruptions in anticoagulation around the time of the procedure. Complication rates have fallen appreciably over the last decade. Despite our best efforts, though, complications will continue to occur. This is a fact, and one that physicians and patients alike must understand before proceeding with AF ablation.

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