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Endovascular Ablation of Atrial Fibrillation

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ATRIAL fibrillation (AF) is the most common cardiac arrhythmia encountered in adults. The estimated overall AF prevalence in ambulatory populations is 1%, though this percentage is much higher in adults older than 65 yr of age.[1] AF risk factors include the male sex, increasing age, and Caucasian ethnicity (table 1).[1–4] The AF incidence is growing, as the prevalence has increased by over 20% in recent studies.[5] AF-associated morbidity is costly and is secondary to the increased risk of heart failure and stroke.[6] We now review the anesthetic considerations of endovascular ablation for the treatment of AF.

Pathophysiology

Atrial fibrillation is characterized by disorganized electrical and mechanical heart activity that arises in the atria with an accompanying irregular ventricular response. An electrocardiogram is essential to confirm AF, which reveals irregular R-R intervals (in the absence of a complete atrioventricular node blockage), an absence of P waves, and a variable atrial cycle length that is usually less than 200 ms.[7] Electrocardiogram monitoring demonstrates that many episodes of AF are self-terminating and asymptomatic. However, with time, the duration of episodes becomes longer, leading to sustained AF.[8]

Atrial fibrillation development requires both a susceptible substrate and a triggering episode.[7] In the normal electrical conduction pathway, the sinoatrial node is the heart pacemaker. In AF, the trigger to myocardial depolarization predominantly develops in the atria and neighboring pulmonary veins (PVs). The PVs are the most common source of the rapid ectopic beats that trigger AF.[9] Recent evidence suggests that once AF is triggered, the arrhythmia is sustained by localized rotors (continuous sequential activation rotating around a central region) and repetitive focal beats sources (activation radiating from a source region).[10]

The atrioventricular node has decremental conduction, meaning that it conducts slower when it receives signals faster. This is protective in AF, it impedes the conduction of rapid atrial signals (300 to 600 beats/min) to the ventricles, and only a portion of the abnormal impulses reach the ventricles (90 to 170 beats/min).[11] Atrial impulses that penetrate the atrioventricular node, but are not propagated to the ventricles, may prolong conduction of the next atrial impulse, known as the concealed conduction phenomenon. As such, the ventricular response is irregularly irregular in AF.[12]

During AF, rapid and chaotic impulses propagate in different directions causing disorganized and quick atrial depolarization, resulting in a hasty quivering rather than forceful contractions of the upper chambers (fibrillation).[13] As a result, the atrial volume is incompletely ejected leading to blood stagnation in the left atrial (LA) appendage. Thus, thrombus formation is promoted, increasing the risk of embolic stroke.

Treatment

Multiple medical AF management strategies have been proposed. Debate exists on whether conversion to sinus rhythm with antiarrhythmic medications is more beneficial than controlling the patient's heart rate along with adequate anticoagulation. The evidence suggests that using medications to achieve sinus rhythm has similar mortality as compared with rate control plus anticoagulation.[14] However, it should be noted that rate control coupled with anticoagulation is

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Table 1. Risk Factors for Atrial Fibrillation[1–4]

Hypertension (most common underlying disorder for patients with atrial fibrillation)	Coronary artery disease/acute myocardial infarction
Congestive heart failure	Valvular heart disease
Congenital heart disease (*i.e.*, ASD)	Obesity (BMI >30 kg/m²)
Diabetes mellitus (risk for atrial fibrillation increases with longer diabetes mellitus duration and higher HbA1c levels)	Thyroid dysfunction
Sex (men > women)	Cardiac surgery, particularly after combined procedures (*i.e.*, bypass grafting + valvular surgery)
Race (more prevalent among Caucasians than African Americans)	Decreased magnesium levels
Heavy alcohol consumption	Family history of atrial fibrillation in a first-degree relative

ASD = atrial septal defect; BMI = body mass index; HbA1c = hemoglobin A1c.

not a treatment plan devoid of side effects. Warfarin, which has traditionally been the primary oral anticoagulant in AF patients, requires constant monitoring of international normalized ratio values, and many patients struggle to achieve therapeutic levels. New oral anticoagulants have been introduced (*e.g.*, dabigatran etexilate, rivaroxaban, and apixabane doxaban) which may increase the efficacy of anticoagulation, but they too are not devoid of complications and currently have no available reversing agents. In an aging population that may be prone to falls or other accidents, anticoagulation may result in devastating bleeding complications.

Catheter Ablation

Radiofrequency catheter ablation (RFCA) has revolutionized the treatment of drug-refractory AF. The aim of RFCA is to prevent AF by identifying and ablating the regions of the heart that are responsible for initiating AF. According to current guidelines, catheter ablation is a first-line treatment in patients with paroxysmal AF and who have minimal or no underlying heart disease. RFCA remains a second-line treatment for symptomatic AF, in which the patient is refractory or intolerant to at least one class 1 or class 3 antiarrhythmic drug.[7]

Isolation of the PVs is the corner stone of catheter ablation strategies for AF treatment.[9] For paroxysmal AF, circumferential PV isolation alone is the standard therapy (figs. 1 and 2). However, ablation of persistent AF is more difficult and requires identification of additional ablation sites using a stepwise approach: (1) Circumferential PV isolation; (2) Ablation of complex fractionated atrial electrograms identified during electrophysiological mapping; (3) Identification and ablation of additional linear lesions. These additional linear lesions may result in ablations along the posterior of the LA, along the roofline of the LA from the left superior PV to the right superior PV, and along the mitral isthmus line connecting the ostium of the left inferior PV to the mitral valve annulus; (4) Ablation of non-PV triggers, such as the coronary sinus, superior vena cava, and crista terminalis.[7] Current estimates of the RFCA success rate at 1 yr for patients with long-standing, persistent AF or paroxysmal AF range from 47 to 74%, respectively.[15,16]

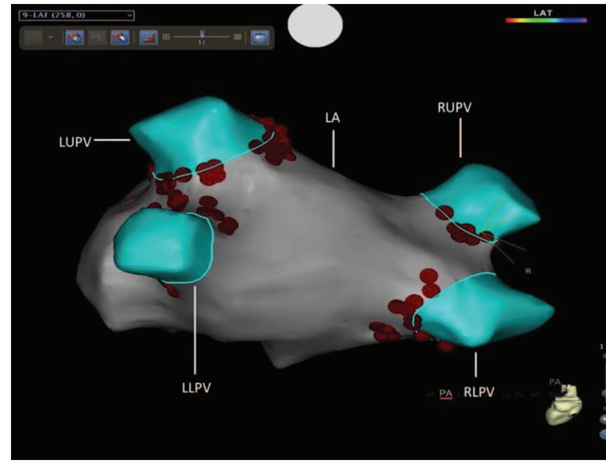

Fig. 1. Electrophysiological map of pulmonary vein ablation sites; *red dots* are the ablation site. LA = left atrium; LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; RLPV = right lower pulmonary vein; RUPV = right upper pulmonary vein.

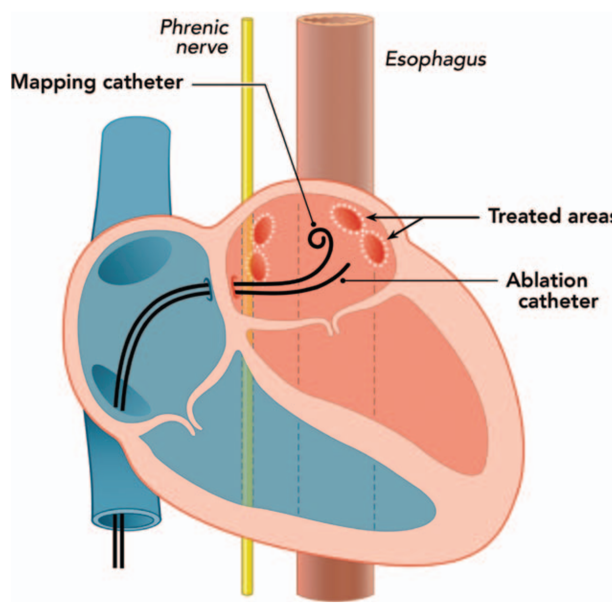

Fig. 2. Ablation sites and pulmonary veins in relation to other anatomic structures.

Radiofrequency catheter ablation generally begins with the placement of femoral venous sheaths used to access the heart. Two 8-French venous sheaths are usually placed in the right femoral vein, and a 7-French along with an 11-French venous sheath is placed into the left femoral vein. The two 8-French sheaths are used as conduits for trans-septal catheters, which are inserted into the right atrium and subsequently across the septum into the LA. These catheters serve the dual purpose of mapping the LA and ablating the desired regions of the heart. Trans-septal puncture is typically performed under intracardiac echocardiographic and fluoroscopic guidance. The intracardiac echocardiographic catheter is inserted *via* an 11-French sheath and is used to confirm the passage of the needle into the LA. The remaining 7-French sheath is used for a coronary sinus catheter, through which additional mapping and pacing can be performed.

After the ablation is completed and the patient is in sinus rhythm, the patient is given a pharmacological challenge before removing the venous sheaths. Isoproterenol, which is known to increase pacemaker activity and abnormal automatism, is typically given at a rate of 2 to 10 μg/min. In addition, adenosine is administered in 6-mg boluses after each PV is isolated with the goal of shortening the atrial refractory period and unmasking reentrant activity originating in the PVs. If either of these medications provokes recurrence of AF, further ablation is performed to ensure optimal results.

More recently, the use of stereotaxis-guided ablation has become widespread. Rather than having individuals manually insert and position the catheters in the heart for ablation, this technique involves using magnetic catheters, which are then steered into position *via* a magnetic navigational device. These catheters are more compliant than the usual stiff RFCA catheters, making them less likely to perforate the heart. In addition, these magnetic catheters offer greater stability allowing for otherwise-difficult ablation of regions with complex anatomy. Finally, less fluoroscopy is required to complete stereotaxis-guided procedures, leading to less radiation exposure for the patient and staff. Although data on success rates have been mixed, some practitioners have reported up to 80% 1-yr success rates using this method.[17]

Similarly, robot-assisted atrial ablation has become more prevalent. With this technology, the operator is able to place and navigate ablation catheters *via* a remote-controlled robotic station. Using the robot, a physician can achieve adequate tissue contact with the catheter using the desired amount of force, theoretically leading to more effective tissue burning. Much like stereotaxis-guided ablation, robot-assisted ablation decreases fluoroscopy time, and overall success rates seem to be similar to that of manual ablation.[18]

Although radiofrequency energy remains the most common energy source used for ablation of AF, cryoablation is now commonly used as an alternative. The success rate of cryoablation during a 12-month period has been reported as high as 73%, with significantly more patients free of recurrent AF than those undergoing pharmacologic therapy.[19,20] During cryoablation procedures, liquid nitrous oxide is delivered through a catheter into a balloon and is subsequently converted into a gas. The gaseous form of nitrous oxide within the balloon acts as a coolant, which ultimately freezes the desired tissue and disrupts cellular function.

One important factor to consider when performing cryoablation within the heart is the blood flow around the region of interest. Increased blood flow near the tip of the balloon can decrease the magnitude of cooling achieved in the tissue because of redistribution of heat. This can lead to difficulty in achieving a full-thickness lesion, which would subsequently reduce the likelihood for a successful procedure. As a result, it is necessary to completely occlude the PVs with the cryoablation balloon to reduce blood flow and allow an adequate lesion to be created. The placement of balloons within the PVs can be a source of potential complications.[20]

Preoperative Considerations

A thorough preoperative evaluation of the patient undergoing RFCA is necessary to ensure patient safety, including a complete history and physical exam. Pertinent information to elicit includes the status of the patient's AF history, such as whether the patient has paroxysmal or chronic AF. Obtaining a complete cardiac history including any underlying risk factors for AF is of high importance. A $CHADS_2$ score, which is a composite number that takes into account the presence of congestive heart failure, hypertension, increased age, diabetes mellitus, and previous stroke, should be calculated to further assess stroke risk (table 2).[21]

All ancillary studies should be reviewed. In particular, any recent echocardiogram (transthoracic or transesophageal) should be examined because comorbid valvular pathologies (*i.e.*, mitral stenosis) may have a profound effect on the anesthetic management of the patient. Obtaining a preoperative transesophageal echocardiogram to rule out intracardiac thrombus is controversial because there seems to be no consensus among experts in the field as to whether it is necessary. Several factors should be considered, including AF duration, the presence of systemic anticoagulation, the patient's $CHADS_2$ score, and LA size, because these are all determinants of the risk of a thromboembolic event.[7] The higher the risk for stroke, the lower the threshold should be to perform a preoperative transesophageal echocardiogram. Despite receiving therapeutic anticoagulation, fewer than 2% of patients will still have thrombus in the LA appendage, with increasing thrombus frequencies seen with higher $CHADS_2$ scores.[22]

Type of Anesthesia

Atrial ablation has been performed successfully under both monitored anesthesia care and general anesthesia (GA). Advantages of proceeding with monitored anesthesia care

Table 2. $CHADS_2$ Scoring System for Predicting the Risk of Stroke in Patients with Atrial Fibrillation.[21,22]

	CHADS2	Points
(C)	Congestive heart failure	1
(H)	Hypertension	1
(A)	Age ≥75	1
(D)	Diabetes mellitus	1
(S_2)	Stroke/transient ischemic attack/ systemic thromboembolism	2

include the ability to avoid volatile and other intravenous anesthetics, which may have adverse effects on the patient's hemodynamic stability. However, AF ablation may last for several hours, and patient discomfort from lying on a table for a long period of time, as well as pain from the procedure itself may preclude choosing this option. This point is particularly important because any patient movement may result in the need for remapping of the patient's arrhythmia and decrease the procedure efficacy.

The choice of which anesthetic technique to use is often institutional, and both methods can be effective. In a prospective study of 650 patients, the use of midazolam, fentanyl, and propofol was used to successfully sedate patients for atrial ablation procedures, with none of the patients requiring endotracheal intubation.[23] In a separate study comparing GA *versus* monitored anesthesia care, the authors concluded that GA was effective in reducing the incidence of PV reconnection when compared with the use of deep sedation.[24]

Intraoperative Considerations

Standard American Society of Anesthesiology monitors are mandatory for this procedure; these include 5-lead electrocardiogram leads, a pulse oximeter, and a noninvasive blood pressure cuff. Measuring end-tidal carbon dioxide concentrations, both qualitatively and quantitatively, remains essential. Arterial line placement is generally recommended; however, it depends on the patient's comorbidities and the likelihood for and duration of arrhythmias during the procedure. Central venous access is not necessary as long as large-bore (16 gauge or larger) intravenous access can be obtained. Defibrillator pads should be placed on the patient and checked to ensure proper positioning before starting the procedure.

Sudden changes in arterial blood pressure should be anticipated because the cardiologist may induce arrhythmias while manipulating the heart. Resuscitation with intravenous fluids may be necessary to compensate for poor filling of the ventricles. However, crystalloids or colloids must be administered with caution in patients with underlying cardiac dysfunction. This is magnified by the fact that patients may receive several liters of fluid during the procedure from the ablation catheters. As a result, overaggressive volume resuscitation can precipitate heart failure with subsequent postoperative intubation and intensive care unit admission.

Anticoagulation

Anticoagulation is necessary during AF ablation. Because of the trans-septal passage of the electrode catheter from the right atrium into the LA, thrombi can form and are at risk systemic embolization.[25] The frequency of stroke during catheter ablation procedures is reported to be approximately 0.4 to 1%.[26,27] However, a literature review does not identify a preferred method to achieve adequate anticoagulation. One recommended anticoagulant regimen involves the issuance of a heparin bolus of 100 U/kg (either before or immediately after trans-septal puncture) followed by an infusion of heparin with the goal of an activated clotting time of 300 to 400 s.[7] An initial heparin bolus and infusion is used to achieve a target activated clotting time of 275 to 350 s; this goal does not change regardless of the patient's anticoagulation status before the procedure. To further reduce the risk of thromboembolism, the trans-septal sheath should be withdrawn into the right atrium once the catheter is positioned, because the sheath is a prominent spot for thrombus formation. The heparin infusion can be discontinued once the catheter has been removed from the atrium. Protamine may be used to reverse the anticoagulation at the end of the procedure. Alternatively, the activated clotting time can be allowed to decrease to its baseline level without protamine reversal before sheath removal.

Esophageal Injury

Injury to the esophagus is a serious RFCA-associated complication, although it less commonly can occur with cryoablation as well. The esophagus is in close proximity to the posterior wall of the LA, where much of the radiofrequency current is directed (fig. 2). The mechanism of injury is thought to be because of direct thermal injury stemming from this current; however, it may be multifactorial. The most devastating type of injury is an atrial-esophageal fistula. The frequency of this type of fistula is extremely low, with a reported incidence rate of 0.2%.[28] Atrial-esophageal fistula may lead to air emboli and sepsis; accordingly, it carries an extremely high mortality rate. If suspected, early surgical intervention or an esophageal stent can be placed. A more common esophageal complication is an esophageal ulcer, which may occur in up to 12% of cases.[29] Esophageal ulcers can generally be managed conservatively without surgical intervention.

Given the morbidity that can be associated with severe esophageal damage, it is essential to monitor for signs of these injuries occurring. One purported advantage of doing RFCA under monitored anesthesia care is that pain can act as an indicator of possible esophageal injury. However, pain during this procedure can reflect several different conditions and, depending on the patient's level of sedation, he or she may not be able to respond to questions regarding pain in an effective manner. One of the most common ways to reduce the risk of esophageal injury in a patient under GA is with the use of an esophageal temperature probe. The esophageal temperature probe can be positioned under fluoroscopy into a position close to the ablation catheter. A sudden increase in temperature requires stopping radiofrequency energy delivery temporarily, reducing the radiofrequency energy, or repositioning the ablation catheter.[29]

Bleeding

Cardiac tamponade complicates atrial ablation procedures in approximately 1.3% of cases and is thought to be the leading cause of death.[26,30] Aspects of the procedure that place patients at increased risk for this complication include improper trans-septal punctures, increased catheter manipulation, and systemic anticoagulation. Any sudden increase in hemodynamic instability (especially if associated with an increase in central venous pressure) should warrant concern about possible severe bleeding or cardiac tamponade. Intraoperative echocardiography is the optimal method to confirm or rule out this diagnosis. If cardiac tamponade is diagnosed, initial treatment is supportive. Infusion of vasopressors and fluids, including blood and component therapy, may be necessary. Additionally, close communication with the cardiology team is necessary to coordinate any reversal of anticoagulation with the presence of catheters within the heart. The cardiologist can place a pericardial drain if the pericardial effusion is large or resulting in hemodynamic instability. If the bleeding continues unabated despite reversal of anticoagulation, definitive surgical treatment may be needed.

Phrenic Nerve Injury

Phrenic nerve injury reportedly occurs in 4.4 to 7.5% of cases.[31,32] Similar to esophageal injury, phrenic nerve injury is thought to result from thermal injury. Phrenic nerve damage results in symptoms ranging from hiccups to dyspnea and chest pain. These injuries typically occur during cryoablation procedures as opposed to radiofrequency ablation. Notably, it is thought that smaller balloons, which can be placed more distally into the PV, have a greater likelihood of causing phrenic nerve injury than larger balloons.[32] The right phrenic nerve is more likely to be affected than the left because it is found anatomically near the right superior PV, a common site for ablation (fig. 2). Accordingly, when the right superior PV is ablated (particularly if cryoablation is to be used), strategies to prevent phrenic nerve injury should be considered. At the Texas Heart Institute, a catheter is inserted into the superior vena cava *via* the right atrium to pace the right phrenic nerve during cryoablation of the right-sided PVs. Manual and fluoroscopic monitoring of diaphragmatic movement is performed at this time; if the motion slows or ceases, ablation is stopped at least temporarily, which generally causes resumption of normal phrenic nerve activity. These preventative tactics will necessitate avoidance of neuromuscular blockade drugs (or the use of anticholinesterase inhibitors to reverse existing blockade) to adequately assess for nerve stimulation.

Air Embolism

Air embolism may occur during atrial ablation.[33] Air may be introduced into the trans-septal sheath and subsequently gain access to the systemic circulation *via* the LA. However, an atrio-esophageal fistula can also cause an air embolism and, given the fistula's high associated morbidity rate, should be ruled out if air embolism is encountered.[28,34] Treatment for a presumptive air embolism is mostly supportive, which includes maintaining hemodynamic stability with fluids and vasoactive agents, pacing the heart if conduction blocks occur, increasing the patient's inspired oxygen level, and putting the patient in trendelenburg.

Postoperative Care

If the case was performed under GA, an attempt to extubate the patient should be made in the majority of cases at the conclusion of the case. However, if there are concerns about a patient's cardiac stability or bleeding status, the patient can be kept intubated and taken to the recovery area or intensive care unit. The presence of excessive bleeding in the postoperative period should be aggressively investigated. If bleeding occurs around the heart, cardiac tamponade may ensue. However, if a patient appears to be hypovolemic despite a negative transthoracic or transesophageal echocardiogram, the patient may be having a retroperitoneal hemorrhage as a result of trauma to the femoral or iliac artery. Retroperitoneal injury may require administration of blood and possibly surgical repair. Fortunately, significant retroperitoneal bleeding is rare, occurring in only 0.07% of atrial ablation patients.[35]

Further complicating the matter is the need for postoperative anticoagulation. After ablation, the atria can be stunned, causing the myocardium to become a fertile ground for thrombi to form. Consequently, anticoagulation should be resumed 4 to 6 h after femoral sheaths from the procedure have been removed.[36] However, this guideline does not apply in the face of continued postoperative bleeding, and anticoagulation should not be resumed until the patient's bleeding diathesis has subsided.

Long-term Outcomes

One-year success rate after first ablation in patients with paroxysmal AF, regardless of source of energy or method of ablation, is approximately 70%.[15,16,19,20] The success rate decreases to less than 50% after 1 yr in patients with nonparoxysmal AF.[15] After a failed first ablation procedure, redo ablation is superior to antiarrhythmic drug therapy.[37] For redo procedures in patients with paroxysmal AF, RFCA results in better outcomes when compared with cryoablation with 1-yr success rates of 58 and 43%, respectively.[38] Other options after failed initial catheter ablation are surgical maze, atrioventricular node ablation, and pacing.

Conclusion

Catheter ablation for AF (RFCA or cryoablation) has become an increasingly common tool in the management of refractory AF. Proper management of the patient undergoing AF ablation requires an understanding of the techniques used and the patient's comorbid conditions. Knowledge of the common complications associated with each procedure and how to monitor for these complications is imperative to ensure patient safety.

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Competing Interests

The authors declare no competing interests.

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References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE: Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370–5
2. Gbadebo TD, Okafor H, Darbar D: Differential impact of race and risk factors on incidence of atrial fibrillation. Am Heart J 2011; 162:31–7
3. Psaty BM, Wiggins KL, Page RL, Heckbert SR: Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med 2010; 25:853–8
4. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A, Calkins H, Connolly SJ, Curtis AB, Darbar D, Ellinor PT, Go AS, Goldschlager NF, Heckbert SR, Jalife J, Kerr CR, Levy D, Lloyd-Jones DM, Massie BM, Nattel S, Olgin JE, Packer DL, Po SS, Tsang TS, Van Wagoner DR, Waldo AL, Wyse DG: Prevention of atrial fibrillation: Report from a national heart, lung, and blood institute workshop. Circulation 2009; 119:606–18
5. Majeed A, Moser K, Carroll K: Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994–1998: Analysis of data from the general practice research database. Heart 2001; 86:284–8
6. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D: Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998; 98:946–52
7. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen S, Crijns H, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Lesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim Y, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012; 14:528–606.
8. Schotten U, Verheule S, Kirchhof P, Goette A: Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. Physiol Rev 2011; 91:265–325
9. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339:659–66
10. Narayan SM, Krummen DE, Rappel WJ: Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol 2012; 23:447–54
11. Patterson E, Scherlag BJ: Decremental conduction in the posterior and anterior AV nodal inputs. J Interv Card Electrophysiol 2002; 7:137–48
12. Meijler FL, Jalife J: [Electrophysiology of the atrioventricular node during atrial fibrillation. II. The influence of atrial impulses]. Ned Tijdschr Geneeskd 1999; 143:1252–6
13. Porth CM: Pathophysiology: Concepts of Altered Health States, 7th edition. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 592–3
14. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators: A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347:1825–33
15. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P: Outcomes of long-standing persistent atrial fibrillation ablation: A systematic review. Heart Rhythm 2010; 7:835–46
16. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators: Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial. JAMA 2010; 303:333–40
17. Katsiyiannis WT, Melby DP, Matelski JL, Ervin VL, Laverence KL, Gornick CC: Feasibility and safety of remote-controlled magnetic navigation for ablation of atrial fibrillation. Am J Cardiol 2008; 102:1674–6
18. Di Biase L, Wang Y, Horton R, Gallinghouse GJ, Mohanty P, Sanchez J, Patel D, Dare M, Canby R, Price LD, Zagrodzky JD, Bailey S, Burkhardt JD, Natale A: Ablation of atrial fibrillation utilizing robotic catheter navigation in comparison to manual navigation and ablation: Single-center experience. J Cardiovasc Electrophysiol 2009; 20:1328–35
19. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, Thibault B, Talajic M, Roy D, Dubuc M: Efficacy and safety of cryoballoon ablation for atrial fibrillation: A systematic review of published studies. Heart Rhythm 2011; 8:1444–51
20. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators: Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: First results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013; 61:1713–23
21. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ: Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–70
22. Puwanant S, Varr BC, Shrestha K, Hussain SK, Tang WH, Gabriel RS, Wazni OM, Bhargava M, Saliba WI, Thomas JD, Lindsay BD, Klein AL: Role of the $CHADS_2$ score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. J Am Coll Cardiol 2009; 54:2032–9
23. Kottkamp H, Hindricks G, Eitel C, Müller K, Siedziako A, Koch J, Anastasiou-Nana M, Varounis C, Arya A, Sommer P, Gaspar T, Piorkowski C, Dagres N: Deep sedation for catheter ablation of atrial fibrillation: A prospective study in 650 consecutive patients. J Cardiovasc Electrophysiol 2011; 22:1339–43

24. Di Biase L, Conti S, Mohanty P, Bai R, Sanchez J, Walton D, John A, Santangeli P, Elayi CS, Beheiry S, Gallinghouse GJ, Mohanty S, Horton R, Bailey S, Burkhardt JD, Natale A: General anesthesia reduces the prevalence of pulmonary vein reconnection during repeat ablation when compared with conscious sedation: Results from a randomized study. Heart Rhythm 2011; 8:368–72
25. Maleki K, Mohammadi R, Hart D, Cotiga D, Farhat N, Steinberg JS: Intracardiac ultrasound detection of thrombus on transseptal sheath: Incidence, treatment, and prevention. J Cardiovasc Electrophysiol 2005; 16:561–5
26. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A: Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. J Am Coll Cardiol 2009; 53: 1798–803
27. Gaita F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, Boffano C, Gandini G, Valentini MC, De Ponti R, Halimi F, Leclercq JF: Radiofrequency catheter ablation of atrial fibrillation: A cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010; 122:1667–73
28. Cummings JE, Schweikert RA, Saliba WI, Burkhardt JD, Kilikaslan F, Saad E, Natale A: Brief communication: Atrial-esophageal fistulas after radiofrequency ablation. Ann Intern Med 2006; 144:572–4
29. Tilz RR, Chun KR, Metzner A, Burchard A, Wissner E, Koektuerk B, Konstantinidou M, Nuyens D, De Potter T, Neven K, Fürnkranz A, Ouyang F, Schmidt B: Unexpected high incidence of esophageal injury following pulmonary vein isolation using robotic navigation. J Cardiovasc Electrophysiol 2010; 21:853–8
30. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, Arya A, Husser D, Rallidis LS, Kremastinos DT, Piorkowski C: Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: Still cause for concern? J Cardiovasc Electrophysiol 2009; 20:1014–9
31. Kuck KH, Fürnkranz A: Cryoballoon ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2010; 21:1427–31
32. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, Kurzidim K, Berkowitsch A, Koller M, Heintze J, Scholz U, Wetzel U, Schneider MA, Horstkotte D, Hamm CW, Pitschner HF: Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol 2008; 52:273–8
33. Hinkle DA, Raizen DM, McGarvey ML, Liu GT: Cerebral air embolism complicating cardiac ablation procedures. Neurology 2001; 56:792–4
34. Pappone C, Oral H, Santinelli V, Vicedomini G, Lang CC, Manguso F, Torracca L, Benussi S, Alfieri O, Hong R, Lau W, Hirata K, Shikuma N, Hall B, Morady F: Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. Circulation 2004; 109:2724–6
35. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A: Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: Results from a multicenter study. Heart Rhythm 2009; 6:1403–12
36. Wazni OM, Beheiry S, Fahmy T, Barrett C, Hao S, Patel D, Di Biase L, Martin DO, Kanj M, Arruda M, Cummings J, Schweikert R, Saliba W, Natale A: Atrial fibrillation ablation in patients with therapeutic international normalized ratio: Comparison of strategies of anticoagulation management in the periprocedural period. Circulation 2007; 116:2531–4
37. Pokushalov E, Romanov A, De Melis M, Artyomenko S, Baranova V, Losik D, Bairamova S, Karaskov A, Mittal S, Steinberg JS: Progression of atrial fibrillation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation: A randomized comparison of drug therapy *versus* reablation. Circ Arrhythm Electrophysiol 2013; 6:754–60
38. Pokushalov E, Romanov A, Artyomenko S, Baranova V, Losik D, Bairamova S, Karaskov A, Mittal S, Steinberg JS: Cryoballoon *versus* radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2013; 24:274–9