State-of-the-art and emerging technologies for atrial fibrillation ablation

Jane Dewire and Hugh Calkins

Abstract | Catheter ablation is an important treatment modality for patients with atrial fibrillation (AF). Although the superiority of catheter ablation over antiarrhythmic drug therapy has been demonstrated in middle-aged patients with paroxysmal AF, the role the procedure in other patient subgroups—particularly those with long-standing persistent AF—has not been well defined. Furthermore, although AF ablation can be performed with reasonable efficacy and safety by experienced operators, long-term success rates for single procedures are suboptimal. Fortunately, extensive ongoing research will improve our understanding of the mechanisms of AF, and considerable funds are being invested in developing new ablation technologies to improve patient outcomes. These technologies include ablation catheters designed to electrically isolate the pulmonary veins with improved safety, efficacy, and speed, catheters designed to deliver radiofrequency energy with improved precision, robotic systems to address the technological demands of the procedure, improved imaging and electrical mapping systems, and MRI-guided ablation strategies. The tools, technologies, and techniques that will ultimately stand the test of time and become the standard approach to AF ablation in the future remain unclear. However, technological advances are sure to result in the necessary improvements in the safety and efficacy of AF ablation procedures.

Dewire, J. & Calkins, H. *Nat. Rev. Cardiol.* **7**, 129–138 (2010); doi:10.1038/nrcardio.2009.232

Introduction

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia, affecting more than 3 million people in the US.[1] AF causes symptoms that impair quality of life, increases the risk of stroke fivefold, and also increases mortality. There are two general approaches to the treatment of AF, rate control and rhythm control. Rate control strategies accept the presence of AF and are directed only at reducing the ventricular response to the arrhythmia. Rhythm control strategies are aimed at the restoration of sinus rhythm and the prevention of AF recurrence. When a rhythm control strategy is chosen, the initial approach is to use antiarrhythmic medications to treat the patient with AF.[1,2] If these agents are ineffective or poorly tolerated, catheter ablation of AF is a reasonable next step. The cornerstone of most catheter ablation approaches is to electrically isolate the pulmonary veins (PVs).[2] These vessels have been demonstrated to be the origin of bursts of atrial tachycardia, which trigger AF (Figure 1).

In the past 10 years, catheter ablation has evolved from a highly investigational technique to its current role as a very commonly performed procedure for the treatment of patients with symptomatic AF.[2] In this Review, we will evaluate current AF ablation strategies and the outcomes associated with these procedures. We will also identify unanswered questions about the current clinical role of AF ablation and discuss the status of emerging technologies, approaches, and tools that are being developed in the field of AF ablation.

Current techniques and outcomes

After more than 5 years of debate about the various approaches to AF ablation, a consensus on this important issue has finally been achieved. As outlined in the Heart Rhythm Society (HRS) consensus document, which was published in June 2007, electrical isolation of the PVs is now recognized as the cornerstone of AF ablation.[2] At most centers where AF ablation is performed, a strategy of creating a series of point-by-point radiofrequency lesions that encircle the two left and two right PVs is used. This procedure is most commonly used in patients with paroxysmal AF.[2] The creation of a linear ablation lesion between ipsilateral superior and inferior PVs, resulting in one or two figure-of-eight lesions depending on the patient's precise PV anatomy, has become an increasingly favored approach (Figure 2). Irrigated radiofrequency ablation catheters are the most common type of ablation catheter used, although 8 mm tipped radiofrequency ablation catheters are preferred at some centers. Three-dimensional (3D) mapping systems, which allow integration of pre-acquired MRI or CT images of the left atrium and PVs, are also employed at many centers. Furthermore, the use of a circular multipolar electrode catheter to confirm electrical isolation of the PVs is now common practice.

Competing interests
H. Calkins declares associations with the following companies: Ablation Frontiers, Biosense Webster, Medtronic, and Sanofi-Aventis. See the article online for full details of the relationships. J. Dewire declares no competing interests.

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Key points

- Catheter ablation is a commonly performed procedure for the treatment of atrial fibrillation (AF)
- Electrical isolation of the pulmonary veins is the cornerstone of most AF ablation procedures
- The use of an irrigated ablation catheter, in conjunction with an electroanatomic mapping system, is currently the most common approach to AF ablation
- New technologies and tools are being developed to make catheter ablation of AF safer and more effective, and to decrease the time and technical skill required to perform the procedure

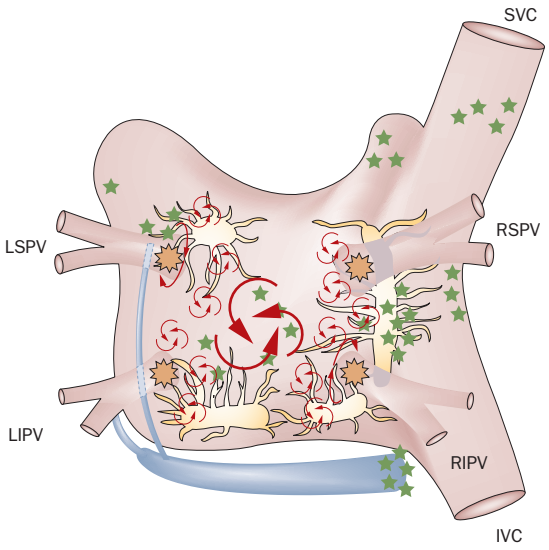

Figure 1 | The anatomical and arrhythmic mechanisms of atrial fibrillation. The left and right atria are viewed from the posterior. The four major left atrial autonomic ganglionic plexi and axons (superior left, inferior left, anterior right, and inferior right) are shown in yellow. The coronary sinus, which is enveloped by muscular fibers that have connections to the atria, and the vein and ligament of Marshall, which travels from the coronary sinus to the region between the left superior pulmonary vein and the left atrial appendage, are shown in blue. Large and small re-entrant wavelets that play a role in initiating and sustaining AF are shown in red. Common origins of pulmonary vein (orange) and non-pulmonary-vein triggers (green) are also shown. Abbreviations: IVC, inferior vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava. Adapted from Calkins, H. *et al*. HRS/EHRA/ECAS Expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. *Europace* **9**, 335–379 (2007) by permission of Oxford University Press, the European Society of Cardiology, and the European Heart Rhythm Association.

Success rates for AF catheter ablation depend on several variables.[2] Of particular importance are the type of AF (paroxysmal, persistent, or long-standing persistent), the presence or absence of comorbid conditions such as obesity and sleep apnea, the definition of 'success', and the duration of follow-up. The HRS consensus document on AF ablation recommends that 'success' be defined as: "freedom from symptomatic or asymptomatic AF, atrial tachycardia, or atrial flutter lasting 30 s or longer 12 months following AF ablation".[2] A 3-month 'blanking period', in which recurrences of AF or atrial flutter are not counted as failures of the procedure, is recommended.

The efficacy of AF catheter ablation can be derived from a number of different sources. Of particular note is a study reporting the results of two meta-analyses comparing the safety and efficacy of AF catheter ablation with that of antiarrhythmic drug (AAD) therapy.[3] In these meta-analyses, 34 studies of AAD therapy and 63 studies of AF ablation were analyzed. The single procedure success rate of AF ablation in the absence of AAD therapy was 57% (95% CI 50–64%). With multiple AF ablation procedures the success rate increased to 71% (95% CI 65–77%). If the concomitant use of AAD therapy was included in the analysis with AF ablation, a further increase in the success rate to 77% (95% CI 73–81%) was reported. The success rate for AAD therapy alone was 52% (95% CI 47–57%).[3] Major complications of catheter ablation occurred in 4.9% of patients and the rate of complications with AAD therapy was 30%. In addition to these large meta-analyses, there have been at least five prospective, randomized clinical trials that compared the outcomes of AF ablation with those of AAD therapy.[4–7] A meta-analysis of these studies reported that 76% of 214 patients treated with catheter ablation were free from AF during the 12 month follow-up period as compared with 18% of 218 patients randomly assigned to receive AAD therapy.[7] The investigators concluded that there was a more than 3.7-fold higher probability of remaining in sinus rhythm with catheter ablation as compared with antiarrhythmic medications. In the prospective, randomized A4 study,[6] catheter ablation was successful in 89% of patients with AF compared with a 23% success rate for AAD therapy. Notably, a median two AF ablation procedures per patient were necessary in the catheter ablation arm. In our experience, and on the basis of our review of the literature, we estimate the efficacy of a single AF ablation procedure in an 'optimum' candidate with paroxysmal AF to be between 60% and 80%. In less suitable patients, such as those with persistent AF, we estimate the single procedure success rate to be 50–80%, and for patients with long-standing persistent AF of 4 years or more, efficacy would be less than 50%.

Catheter ablation of AF is a demanding and complex interventional electrophysiological procedure that is associated with a considerable risk of major complications. In an international survey of AF ablation, major complications occurred in 6% of procedures.[8] Incidence of cardiac tamponade was 1.2%, stroke or transient ischemic attack (TIA) 0.94%, PV stenosis 1.3%, and death 0.05%.[8] A study from our institution reported a major complication rate of 5%, which included stroke or TIA (1.1%), cardiac tamponade (1.2%), PV stenosis (0.2%), and vascular injury (1.7%).[9] Two large meta-analyses of studies on the use of AF ablation versus AADs reported that catheter ablation was associated with a 4.9%

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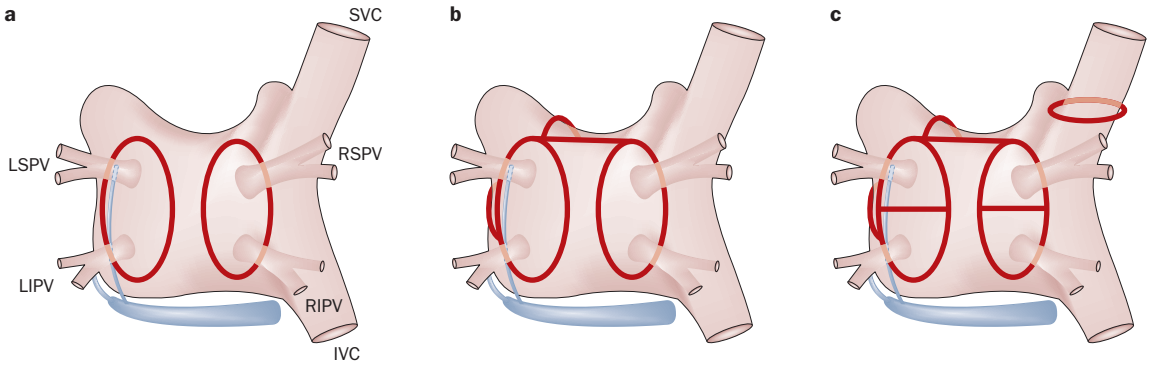

Figure 2 | Schematic of common lesion sets employed in atrial fibrillation ablation. The left and right atria are viewed from the posterior. **a** | Circumferential ablation lesions are created around the right and the left pulmonary veins. The aim of this ablation strategy is the electrical isolation of the pulmonary vein musculature. **b** | Some of the most common sites of linear ablation lesions. These include a "roof line" connecting the lesions encircling the left and/or right pulmonary veins, a "mitral isthmus" line connecting the mitral valve and the lesion encircling the left pulmonary veins at the level of the left inferior pulmonary veins, and an anterior linear lesion connecting either the "roof line" or the left or right circumferential lesion to the mitral annulus anteriorly. **c** | Similar to panel b, but showing additional linear ablation lesions between the superior and inferior pulmonary veins resulting in a figure-of-eight lesion set. Also shown is an encircling lesion of the superior vena cava directed at electrical isolation of the superior vena cava. SVC isolation is performed if focal firing from the SVC can be demonstrated. Abbreviations: IVC, inferior vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava. Adapted from Calkins, H. *et al*. HRS/EHRA/ECAS Expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. *Europace* **9**, 335–379 (2007) by permission of Oxford University Press, the European Society of Cardiology, and the European Heart Rhythm Association.

incidence of major complications as compared with a 30% complication rate for AAD therapy.[3] Of particular note is a report published in May 2009 from an international survey of AF ablation at 162 centers, which documented 32 deaths occurring in 32,569 patients (0.1%) during or following AF ablation procedures.[10] Causes of death included tamponade in eight patients (25% of deaths), stroke in five patients (16%), atrioesophageal fistula in five patients (16%), and pneumonia in two patients (6%). A variety of miscellaneous causes accounted for each of the remaining deaths. On the basis of our clinical experience with AF ablation and our knowledge of the literature, we estimate that the current incidence of major complications lies between 2% and 6%. The incidence of cardiac tamponade would be 0.5–2.0%, stroke or TIA is 0.5–1.0%, vascular injury 0.5–2.0%, and the risk for development of an atrial esophageal fistula or death would be less than 0.1%.

Current frontiers

Although great progress has been made in improving the techniques and outcomes of AF catheter ablation, many challenges remain. One of the most important issues is defining the clinical role of and best approach to catheter ablation in patients with long-standing persistent AF. A second controversy involves the outcomes and clinical role of AF ablation in elderly patients. Thirdly, the role of catheter ablation in patients with heart failure also requires further investigation.

Ablation of long-standing persistent AF

The HRS consensus document recommends that the terms "chronic AF" and "permanent AF" not be used in the context of patients undergoing AF ablation.[2] Instead, the use of the term "long-standing persistent AF", is recommended to describe the subset of AF patients who have been in AF continuously for 12 months or longer.[2] Clearly, to all those involved in this field of research, patient outcomes after AF ablation are substantially worse in those with long-standing persistent AF. However, the optimum ablation strategy for use in this setting has yet to be determined.

A number of different ablation techniques have been proposed for patients with long-standing persistent AF. One approach, which was developed by Nadamanee and colleagues, is to target areas of atrial myocardium demonstrating complex fractionated atrial electrograms (CFAEs; Figure 3).[11,12] Nadamanee *et al.* defined CFAEs as having two or more deflections, perturbation of baseline with continuous deflection of a prolonged activation complex over a 10 s recording period, or both, and as having a very short cycle (≤120 ms) averaged over a 10 s recording period.[11] Importantly, the presence or absence of CFAEs was determined by visual analysis of a single operator and not by an automated software algorithm. The investigators have reported long-term efficacy rates in excess of 70% for this approach.[12] These encouraging results have not, however, been replicated by other researchers.[13] This technique will be discussed in more detail later in the article when we review ablation strategies that target areas other than the PVs.

Other strategies can be broadly referred to as 'PV isolation plus' and are based on achieving PV isolation before performing additional ablation strategies including CFAE ablation the creation of linear lines, or both. These strategies differ from the approach used by Nadamanee and colleagues, outlined above, in that electrical isolation of the PVs is always performed. Haissaguerre *et al.*

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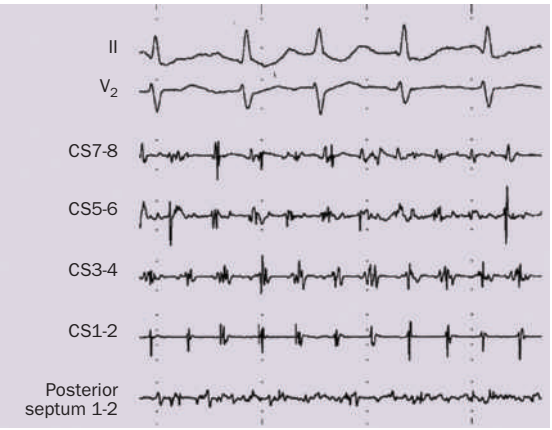

Figure 3 | Complex fractionated atrial electrograms. Showing continuous prolonged activation complex over the posterior septal areas. Abbreviation: CS, coronary sinus. Reprinted from the *Journal of the American College of Cardiology* **43**(11), Nademanee, K. *et al*. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. 2044–2053 © 2004 with permission from Elsevier.

have devised a stepwise approach to AF ablation in patients with long-standing persistent AF.[14,15] The strategy is based on initial PV isolation followed by linear and CFAE ablation in a sequential fashion until AF terminates. These investigators have reported reasonable success rates with this technique, particularly when multiple AF ablation procedures are used in conjunction with amiodarone.[14,15]

Despite the growing enthusiasm for these aggressive ablation strategies, we are of the opinion that the data do not currently support their broad adoption. We prefer a staged approach to AF ablation in patients with long-standing persistent AF, in which the PVs are isolated during the initial ablation procedure. If this is ineffective, patients can undergo a second and more extensive ablation procedure. In our experience, failure of the initial ablation and hence the need for a second procedure, varies based on the duration of continuous atrial fibrillation. Approximately one third of patients with long standing persistent AF of less than 2-years duration undergo a second ablation procedure, compared with approximately 50% of patients with AF that has been continuous for more than 2 years. The advantage of this approach is that the extent of ablation is minimized with the first procedure. And that more aggressive and less proven ablation strategies are withheld until failure of this conservative approach.

AF ablation in elderly patients

Most AF ablation procedures are performed in patients younger than 70 years of age.[2] The safety and efficacy of AF ablation in elderly (aged older than 70 years) and very elderly (aged older than 80 years) patients, therefore, remain uncertain. Although outcome data for these groups of patients are sparse, one study comparing the safety and efficacy of catheter ablation in patients aged younger than 65 years ($n = 948$), aged 65–74 years ($n = 185$), and aged older than 75 years during a 27 month follow-up period found that there were no significant differences in the complication rates between the three groups (1.6%, 1.7%, and 2.9%, respectively).[16] Moreover, comparable AF control rates (89%, 84%, and 86%, respectively) were observed across the age categories.[16] Patients over the age of 75 years were, however, less likely to undergo repeated procedures and preferred to remain on antiarrhythmic medications. Although the results of this study are encouraging, much larger trials are clearly needed before AF ablation should be offered routinely to patients over the age of 75 years.

AF ablation in patients with heart failure

AF and heart failure are two of the greatest unmet challenges in cardiovascular medicine and a close relationship exists between these two conditions. Many patients with heart failure have AF and many patients with AF have heart failure, and the incidence of both conditions is increasing.[1] A number of clinical trials have examined the role of AF catheter ablation in patients with congestive heart failure. The first major study to address this important subject was published in 2004.[17] Hsu *et al.* performed AF catheter ablation in 58 patients who also had heart failure (left ventricular ejection fraction [LVEF] <45%) and in 58 control individuals who did not have heart failure. During follow-up (mean 12 months), 78% of patients with heart failure and 84% of controls remained in sinus rhythm. Of particular note is that the LVEF in patients with heart failure improved by 21%, and improvements in exercise capacity and quality of life were also observed in this group.[17] In another study, the PABA-CHF Trial,[18] the efficacy of AF ablation was compared with atrioventricular node ablation and pacemaker implantation in patients with both AF and HF. Patients who underwent PV isolation had a lower score on the Minnesota Living with Heart Failure Questionnaire (60 versus 82), a longer walking distance on the 6-min walk test (340 m versus 297 m), and higher LVEF (35% versus 28%) than those who underwent atrioventricular node ablation, demonstrating the overall superiority of PV isolation in this setting.[18] Although data on outcomes of AF ablation in patients with heart failure are scarce, the available evidence suggests that catheter ablation of AF is effective in this patient population. However, additional larger clinical trials are clearly needed.

New techniques, tools, and outcomes

Great interest currently exists in the development of new tools and strategies that will improve the safety and efficacy of AF ablation, shorten procedure time, and allow ablation to be performed by operators with little prior experience of the technique. Each of the new ablation technologies are discussed below.

Pulmonary vein based strategies

The current widespread acceptance and success of the PV isolation technique has generated interest in the development of balloon catheters that can be inserted into each of the PVs and used to create ablation lesions by delivering a number of ablation energies. One of the advantages

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of these balloon catheters is that 3D electroanatomic mapping systems are not required. Balloon catheters should, theoretically, be easy to position in the PVs and create a circumferential homogeneous ablation lesion with a single application of energy.

Cryoablation

Cryoablation refers to the use of cryotherapy (freezing) to destroy myocardial tissue. The process of freezing and rewarming myocardial tissue results in cell death. One of the potential benefits of cryoablation is that, unlike radiofrequency energy, myocardial tissue architecture is preserved and could translate into a reduced risk of thromboembolic complications. In addition, cryoablation might be less likely than radiofrequency ablation to result in PV stenosis or esophageal fistula.

CryoCath Technologies has developed Arctic Front® (Medtronic CryoCath LP Ltd, Chemin Ste-Marie Kirkland, QC, Canada), a cryoballoon ablation system that allows for the refrigerant nitrous oxide to undergo a phase change in the inner balloon, cooling the temperature to approximately -80 °C (Figure 4).[19–22] This ablation system is currently approved for clinical use in Europe. A pivotal trial seeking FDA approval has been completed and the results are anticipated in late 2009 or early 2010. A large number of trials have been performed to evaluate the safety and efficacy of the Arctic Front® system. One of the largest of these studies was by Neumann *et al.* and was published in 2008.[21] The outcomes of 346 patients with drug-refractory paroxysmal ($n = 293$) or persistent ($n = 53$) AF were reported. In this trial, 97% of PVs were isolated, either with the Arctic Front® balloon alone or with the balloon in combination with the point-by-point Freezor® Max (Medtronic CryoCath LP Ltd, Chemin Ste-Marie Kirkland, QC, Canada) ablation catheter.[21] The median procedure time was 170 min. During follow-up (median 12 months), sinus rhythm was maintained without the need for AAD therapy in 74% of patients with paroxysmal AF and in 42% of patients with persistent AF. Major complications occurred in 10% of patients, including cardiac tamponade in two patients, and vascular complications in eight patients. Phrenic nerve paralysis occurred in 26 patients, but resolved within 12 months in each of these individuals. No patient developed PV stenosis; there were no strokes, and no cases of atrial esophageal fistula.[21]

Moreira *et al.* reported the long-term outcomes of 70 patients with paroxysmal AF who underwent AF ablation with the CryoCath system (Arctic Front® plus Freezor® Max).[22] An average of five cryoapplications were delivered to each PV. Complications were reported in three patients (4%), including one stroke, one pulmonary embolism, and one patient who developed transient phrenic nerve paralysis. At the end of follow-up (mean 33 months), 49% of patients were free from AF without the need for antiarrhythmic medications, and an additional 22% of patients were free from AF with AAD therapy. Although the results of these initial studies indicate great promise for the CryoCath system, its ultimate clinical value will be defined after FDA approval and with widespread clinical availability. Only then will clinicians throughout the US be able to examine the safety and efficacy of this system at their own centers.

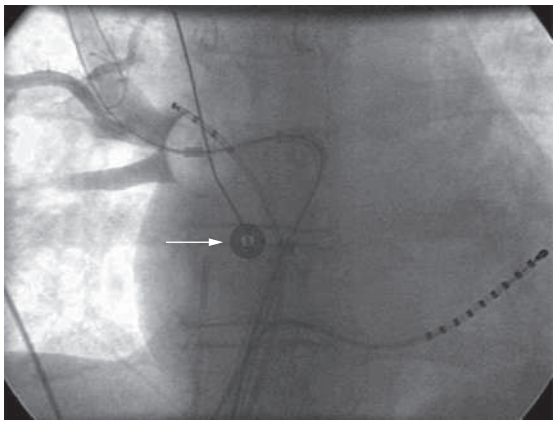

Figure 4 | Occlusion of the right superior pulmonary vein with the Arctic Front® (Medtronic CryoCath LP Ltd, Chemin Ste-Marie Kirkland, QC) cryoballoon catheter (arrow). Also shown are a quadripolar pacing catheter in the superior vena caval–right atrial junction, multipolar mapping catheter in the coronary sinus and an intracardiac echo catheter in the mid-right-atrium. X-ray image taken during contrast fluid injection. Reproduced from Van Belle, Y. *et al*. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcomes. *European Heart Journal*, 2007, Vol. **28**, issue 18, 2231–2237 by permission of Oxford University Press and the European Society of Cardiology.

Laser balloon catheter

The CardioFocus® (Marlborough, MA) ablation system is balloon-based, uses laser energy for ablation, and involves three 20 mm, 25 mm, or 30 mm diameter balloon catheters. A diode laser is used to generate a wave of energy at 980 nm to burn the myocardial tissue for 60 s with an arc length of 6 watts/cm.[23,24] Relatively little data are available on the outcomes of AF ablation using the CardioFocus® system. One study of nine patients reported recurrent AF in three patients within 13 months of follow-up.[23] Major complications, including cardiac tamponade and phrenic nerve paralysis, were observed in two patients.[23] Another small study reported complete PV isolation in all four patients acutely, although one individual experienced AF recurrence during follow-up.[24] There were no reported complications in this small case series. Clearly, more and larger studies will be needed to determine the true safety and efficacy of the CardioFocus® laser balloon ablation system.

HIFU balloon catheter

The high-intensity focused ultrasound (HIFU) balloon catheter (ProRhythm® Inc., Ronkonkoma, NY) uses a focused ring of ultrasound energy to ablate myocardial tissue. This system consists of two noncompliant balloons—one filled with a mixture of water and contrast media and the other filled with carbon dioxide—that form the ultrasound energy ring ~4 mm from the tip of the balloon.[25,26] Two initial trials performed in 2007 evaluated the safety and efficacy of the HIFU balloon and

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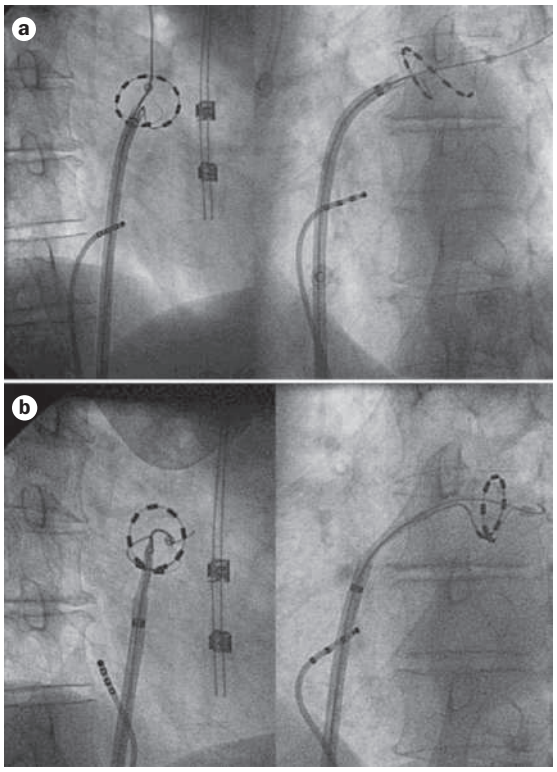

Figure 5 | The Ablation Frontiers® (Carlsbad, CA) pulmonary vein ablation catheter (PVAC). **a** | Biplane fluoroscopic view of the PVAC with electrode array extended in the left superior pulmonary vein. **b** | Biplane fluoroscopic view of the PVAC in the left superior pulmonary vein demonstrating reduced diameter. This configuration was attained by engaging the antrum and then rotating the catheter shaft clockwise. Reprinted from *Heart Rhythm* **5**(12), Boersma, L. V. A. *et al*. Pulmonary vein isolation by duty-cycled bipolar and unipolar radiofrequency energy with a multielectrode ablation catheter. 1635–1642 © 2008 with permission from Elsevier.

demonstrated that this system was successful for PV antra isolation in 87% ($n = 27$)[25] and 89% ($n = 12$)[26] of the targeted PVs. However, in 2008, Borchert *et al.* reported that treatment with the HIFU ablation system led to atrioesophageal fistula in several patients (<1%), resulting in one death.[27] As a consequence of this risk of atrial esophageal fistula, all clinical trials with the ProRhythm® focused ultrasound ablation system have now been terminated.

Multipolar circular ablation catheter

The Ablation Frontiers® (Carlsbad, CA) decapolar PV ablation catheter is another PV-based system that is in development (Figure 5).[28,29] This circular, multipolar ablation catheter creates ablative lesions by delivering both duty-cycled bipolar and unipolar radiofrequency energy at a relatively low power. As with the balloon-based ablation systems described above, a 3D electroanatomic mapping system is not required. The Ablation Frontiers® system has been approved for clinical use in Europe and a prospective, randomized clinical trial comparing this catheter system with AAD therapy in patients with persistent and long-standing persistent AF has completed enrollment in the US.[30] The safety and efficacy of the Ablation Frontiers® ablation system have been evaluated in several studies. Boersma *et al.* examined the outcomes of 98 patients with paroxysmal AF who were treated with this system.[28] All 369 PVs were isolated without any complications (mean procedure time 84 min). At 6 months follow-up, 83% of patients were free from AF.[28] Fredersdorf *et al.* reported acute isolation of 99% of PVs and an 88% success rate at 6 months follow-up in 21 patients who underwent ablation with the Ablation Frontiers® system.[29] The mean procedure time was 84 min and no complications were reported. Although early results with the Ablation Frontiers® system have been encouraging, larger clinical trials with longer follow-up will be needed to determine the true safety and efficacy of this unique system.

High-density mesh ablator

The high-density mesh ablator (HDMA)—also known as the Bard® mesh catheter (Bard Electrophysiology, Lowell, MA)—is another multielectrode PV ablation device (Figure 6). The system consists of twice opposing 18 electrode pairs that are braided together to perform 36-bipole mapping abilities and delivery of radiofrequency energy as well as 36 unipolar or bipolar electrograms.[31–34] This catheter delivers 5 ms pulses of radiofrequency energy in a circumferential fashion with an adjustable diameter that can reach 30 mm. The wire segment of the catheter is divided into four sections, each of which contains a thermocouple to monitor temperature and control energy application. In addition to creating ablation lesions, the HDMA can also be used to anatomically and electrically map the PVs. The safety and efficacy of the HDMA system in both mapping and ablating the PVs have been reported.[31–34] Mapping was 100% successful in all four studies and the success rate for PV isolation was 63%,[31] 97%,[32] and 100%,[33,34] respectively. No procedure-related complications occurred in any of the studies and the mean procedure times were reported as 159 min,[31] 200 min,[32] 270 min,[33] and 187 min.[34] Meissner and colleagues found that 85.6% ($n = 14$) of patients with paroxysmal AF and 41.6% ($n = 12$) of those with persistent AF were asymptomatic 3 months after treatment with the HDMA catheter.[31] Similarly, Filippo *et al.* found that 80% ($n = 10$) of patients with paroxysmal AF and 43% ($n = 7$) of those with persistent AF were free of AF at the end of follow-up (mean 11 months).[32] Although initial results for the HDMA catheter are promising, larger studies with longer-term follow-up will be needed to determine the true safety and efficacy of this ablation system. A randomized, multicenter clinical trial of this system is now underway in the US as part of the FDA approval process.

Strategies not targeting the pulmonary veins

Although isolation of the PVs remains the cornerstone of most current AF ablation procedures, alternative strategies targeting other structures of the heart have been developed and research aimed at improving their safety and efficacy is ongoing.

CFAE-guided ablation

This approach, which was first described by Nademanee and colleagues in 2004,[11] targets areas of myocardium that

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demonstrate CFAEs.[35–39] In their first study, the investigators targeted and eliminated CFAE areas in 57 patients with paroxysmal AF and 64 patients with long-standing persistent AF.[11] After the procedure (mean procedure time ~3.1 h) all of the patients with paroxysmal AF and 91% of the patients with long-standing persistent AF were in sinus rhythm. At 1 year follow-up, 91% of all patients were free from symptomatic AF. These researchers subsequently reported the outcomes of 674 patients who underwent ablation using this approach, 81.4% of whom were in sinus rhythm after 5 years follow-up.[12] However, these impressive results have not been replicated by other groups. In a study by Estner and colleagues, only 9% of 23 patients with persistent AF who underwent CFAE-guided ablation alone were in sinus rhythm without the need for AADs after a single procedure, as compared with 41% of 54 patients who received CFAE-guided ablation plus PV isolation.[35] Additionally, Porter *et al.* reported that ablation targeted at CFAEs eliminated symptoms in 88% of 42 patients with paroxysmal AF, but in only 20% of 25 patients with persistent AF.[36] Most recently, in March 2009, Oral and colleagues reported the effect of CFAE-guided ablation in conjunction with PV isolation in 119 patients with persistent AF.[13] AF terminated during initial PV isolation in 16% of these individuals. No difference in outcomes was observed among the remaining patients, who were randomly assigned to undergo CFAE-guided ablation for up to 60 min or to be cardioverted.[13] These findings cast further uncertainly on the value of CFAE-guided ablation. The subjective nature of defining a CFAE by visual inspection could be a potential reason that other researchers have not been able to replicate the successful results of Nademanee and colleagues. To address this issue, several new software algorithms have been developed to 'automatically' identify CFAE sites.[37–39]

Ablation of ganglionated plexi

The relationship between AF and the autonomic nervous system is another area of intense research. Pappone *et al.* are credited with being the first to report a link between stimulation of the autonomic nervous system during AF ablation and ablation outcome.[40] These investigators reported that one third of patients undergoing AF ablation develop a vagal reflex during AF ablation. This observation was associated with a 99% success rate as compared with an 85% success rate among patients where a vagal reflex was not observed. These results led researchers to further explore the potential role of targeting autonomic ganglia as a stand-alone or adjunctive AF ablation strategy.[40–46]

Several small clinical trials have assessed the efficacy and safety of procedures that target and ablate ganglionated plexi in both humans and dogs, and compared these procedures to circumferential PV isolation.[41,44–46] In 2006, Lemery *et al.* successfully mapped ganglionated plexi in 14 patients with AF, finding that these anatomical structures predominately overlay the PVs.[45] In two single-center studies, catheter ablation of ganglionated plexi was found to be feasible and safe for the treatment of patients with AF.[44,45] However, in another study, 74% of patients who underwent ablation of ganglionated plexi experienced AF recurrence after 1 year compared with 37% of those patients who received conventional circumferential PV isolation.[46] In another study by Danik and colleagues, AF remained inducible in 94% of 18 patients, despite successful ablation of ganglionated plexi.[44] More research is clearly needed to better define the role of catheter ablation of autonomic ganglia in the treatment of patients with AF.

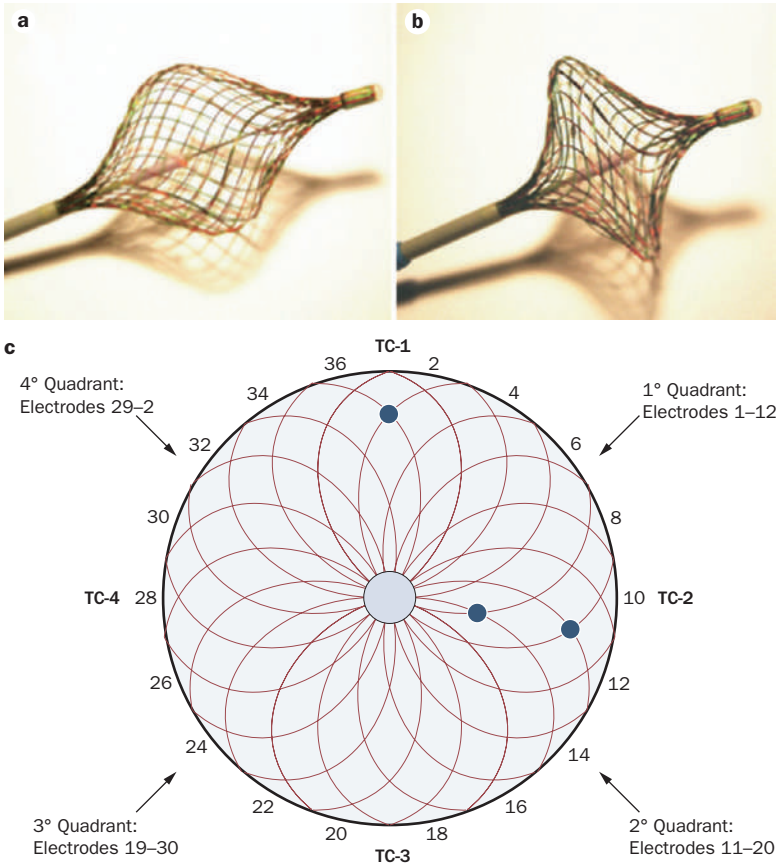

Figure 6 | High-density Mesh ablator (Bard Electrophysiology, Lowell, MA) is built around a Mesh geometry that optimizes contact and signal quality without obstructing blood flow. The catheter contains an annular ring of exposed wire (6 mm wide) at its perimeter that serves as the electrodes for high-resolution recording as well as for delivery of radiofrequency current. The Mesh catheter can be adjusted according to the diameter of the vein. **a** | The partially deployed Mesh ablator is useful for distal mapping, which is generally not desired for ablation unless ablation will be proximal to the electrical ostium and the pulmonary vein is small (<15 mm). **b** | The fully deployed Mesh ablator allows proximal ablation at the pulmonary vein ostia. **c** | Schematic representation of the Mesh design. Frontal view of a fully deployed Mesh ablator. The annular ring is divided into four quadrants each capable of selective radiofrequency deliveries. Each quadrant contains a thermocouple allowing radiofrequency delivery in a temperature-control mode. The three black dots indicate radiological markers to help recognize the orientation of the catheter. Abbreviation: TC, thermocouple. Reprinted from *Heart Rhythm* **5**(11), Mansour, M. *et al*. Initial experience with the Mesh catheter for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. 1510–1516 © 2008 with permission from Elsevier.

Remote, automatic, and robotic navigation

Two automated systems for the mapping and ablation of AF are currently available. The Niobe® (Stereotaxis, Inc., St. Louis, MO) robotic magnetic catheter navigation (RMN) system consists of two computer-controlled, focused-field, permanent magnets placed on either side

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of the patient.[47,48] The magnetic field creates a spherical navigation volume of 20 cm, in which a catheter containing three magnets is introduced and manipulated via the magnetic field vectors. The operator navigates the catheter using a joystick and keyboard commands from a separate control room. Several studies have demonstrated that catheter ablation procedures, including ablation of AF, can be performed using this system.[47–50] Until 2009, irrigated ablation catheters were not available for use in conjunction with the Niobe® system in the US. However, this important limitation was overcome when irrigated ablation catheters were released and are now being used for AF ablation procedures at the many sites with a Niobe® system. At present, the safety and effectiveness of the Niobe® system appear to be similar to conventional ablation tools.[47–50] One study of 40 patients reported a 75% success rate at 12 months follow-up with standard ablation technologies as compared with an 80% success rate when the Niobe® system was used.[50] The future of the Niobe® system will, in our opinion, depend on whether it can improve the safety and efficacy of AF ablation in the hands of experienced and inexperienced operators alike.

The Sensei® X (Hansen Medical, Mountain View, CA) remote robotic navigation system is another technology that is currently being developed. The system is operated with an Instinctive Motion Controller from a remote workstation.[51–53] A remote catheter manipulator receives commands from the Instinctive Motion Controller and controls the movement of a robotic sheath, through which standard ablation catheters can be inserted. Since the release of this system for clinical use, a number of small studies have demonstrated its efficacy and safety for catheter ablation of AF. Schmidt *et al.* reported the use of the Sensei® X system was associated with a 35% reduction in fluoroscopy time for the operator, as well as 76% and 68% success rates for AF ablation in paroxysmal and persistent AF, respectively, at 1 year follow-up.[51] Furthermore, Saliba and colleagues were able to completely isolate the PVs with the Sensei® X system in 40 patients, and at 1 year follow-up reported that 86% were free of AF without the need for AADs and an additional 12.5% of patients were free of AF with these medications.[52]

One of the main concerns with the Sensei® X system is the risk of cardiac tamponade, which has been reported in several series.[51,52] These studies are too small to determine whether the risk of cardiac tamponade is higher with the Sensei® X system than with a conventional approach to ablation, and this issue requires further study. As with the Stereotaxis system, the role of the Sensei® X system in AF ablation will ultimately rest on whether it can improve procedural efficacy, safety, or both, which should become clear in the next 2–5 years.

MRI-guided ablation

Real-time MRI is another technology that is being used to improve the safety and efficacy of AF catheter ablation. In the past 5 years, a number of studies have demonstrated the value of using MRI to image myocardial scar both before ablation, as a predictor of success, and after the procedure.[53,54] Substantial progress has also been made in developing the tools to allow electrophysiological studies and catheter ablation to be carried out while the patient is in the MRI scanner.[55] Notably, a study by Nazarian *et al.* reported the feasibility of using MRI to guide diagnostic electrophysiological procedures,[55] but no studies have yet investigated the use of MRI guidance during catheter ablation. MRI has several potential advantages; it is radiation free, allows imaging of myocardial tissue and structures and ablation lesions, and is similar in cost to a biplane fluoroscopy system. As with many of the other technological advances outlined in this Review, further research is needed before the true clinical value of MRI-guided AF ablation can be evaluated.

Conclusions

Catheter ablation is an important therapeutic modality for patients with AF. Although great progress has been made in improving the safety and efficacy of the procedure, much research is still needed. In our opinion, the greatest challenge at this time is to improve the long-term efficacy of single-procedure catheter ablation of paroxysmal, persistent and, particularly, long-standing persistent AF. Single procedure success rates, which currently vary between 35% and 70%, are suboptimal despite being superior in efficacy to antiarrhythmic medications. We believe that single procedure success rates can and will increase dramatically over the next 5 years to between 70% and 90%. Improvements are likely to be achieved by both technological advances in the tools available to perform AF ablation procedures and increased understanding of the precise pathophysiological basis of AF.

The second greatest challenge in the field of AF catheter ablation is to reduce the risks associated with the procedure. Atrial esophageal fistulas, although very rare (<0.1% of patients) continue to occur. Cardiac tamponade is more common (0.5–2.0% of patients) and accounts for many more deaths than atrial esophageal fistula. Cardiac tamponade is unlikely to ever be completely eliminated, but our goal should be to reduce the risk of this complication (and of stroke and catheter-access-related complications) to less than 1 in 500 procedures.

The progress made in the field of AF catheter ablation is truly remarkable. When radiofrequency catheter ablation of accessory pathways was being developed in the late 1980s, the use of this ablation technology in patients with AF was unimaginable. Now, 20 years on, catheter ablation of AF is the most commonly performed ablation procedure in most major hospitals. If the past predicts the future, our goals will be achieved.

Review criteria

The references used for this Review were selected by performing a PubMed search. Search terms included "catheter ablation", "atrial fibrillation", and "pulmonary vein isolation". Referenced articles were selected on the basis of scientific value and on the time of publication. Only articles in the English language were considered. We also drew from personal experience as well as manuscripts that we have published previously.

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