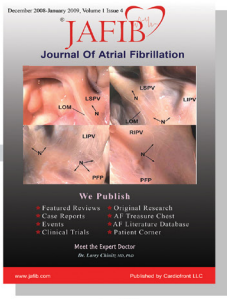
JAFIB
Featured Review
Journal of Atrial Fibrillation



www. jafib.com

Catheter Abalation for AF : Past, Present and Future

David Spragg, MD and Hugh Calkins, MD

Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD USA Asuncion.

Introduction

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered by physicians. The prevalence of AF in patients over the age of 65 is approximately 6%, and approaches 10% in patients over the age of 85.[1] As the median age of the population in the United States becomes older, the epidemiologic burden of AF in this country will likely increase. Currently approximately 2.2 million people in the United States have AF.[1] AF, while typically not a life-threatening arrhythmia per se, is associated with increased risk of stroke,[2] heart failure, and increased mortality. The stroke risk in patients with AF, for instance, is increased between 5- and 7-fold compared to similar patients without AF. [3, 4]

Therapy for AF can be divided into two major paradigms – rate control and rhythm control. Rate control, as the name implies, focuses exclusively on preventing an uncontrolled, rapid ventricular response rate in the setting of AF. Strategies to achieve rate control typically include either pharmacological agents to slow conduction through the atrio-ventricular (AV) node (i.e. beta-blockers or calcium-channel blockers), or ablation of the AV junction and implantation of a permanent pacemaker. Large prospective randomized trials have validated rate control as a reasonable option in patients with AF, particularly in terms of overall mortality.[5, 6] However, such a strategy does nothing to reduce the stroke risk and loss of AV synchrony seen in patients with AF, and as such, represents a suboptimal strategy in many patients.

The second paradigm, rhythm control, has historically involved the use of antiarrhythmic medications and/or DC cardioversion from AF into sinus rhythm. Antiarrhythmic medications used for the maintenance of sinus rhythm include class I and class III agents. Randomized prospective data has demonstrated that amiodarone, compared to other class III and to class I medications, is the most effective antiarrhythmic drug to prevent AF.[7,8] Long-term therapy with amiodarone is imperfect, however, due both to limited efficacy and to attendant end-organ toxicities. Recurrence rates in patients treated with amiodarone are approximately 35%. [7] As importantly, amiodarone has dose-dependent effects on thyroid, liver, and pulmonary function. In patients treated with DC cardioversion alone (i.e. without the suppressive effects of anti-arrhythmic medications) AF recurrence is predictably high, with nearly 66% of cardioverted patients developing recurrent AF within 15 months.[9] In part because of the limitations of effective and safe pharmacological therapy for AF suppression, clinicians have sought non-pharmacological interventions to achieve rhythm control.

Corresponding Address :Hugh Calkins, MD,Johns Hopkins Hospital,Carnegie 530,600 N Wolfe Street,Baltimore,MD 21287-0409.

Over the past 15 years, techniques for catheter-based ablation of atrial fibrillation have evolved, and now provide a widely accepted therapeutic option for the treatment and potential cure of AF. This chapter reviews that evolution, summarizes current trends in practice, and speculates on the future directions of AF ablation.

Catheter-based Treatment For Atrial Fibrillation

In 1959, Moe hypothesized that AF was due to multiple randomly propagating reentrant waves in the atrium, suggesting that functional reentry was the mechanism underlying fibrillation.[10-12] In subsequent work by Allessie and others,[13-15] Moe's hypothesis was confirmed. AF was demonstrated to require at least 6 to 8 circulating reentrant wavefronts. Maintenance of AF depended both on a critical atrial mass and on conduction velocity and refractory periods in the atrial tissue to support functional reentry.

Catheter ablation for atrial tachyarrhythmias is a relatively recent phenomenon.[16-20] The propagation of electrical activation from atria to ventricles over myocardial fibers was originally described in 1883.[21] Nearly a century later, Scheinman and colleagues described the first catheter-based ablation procedure – His bundle interruption for the control of ventricular response rates to refractory supraventricular tachycardias.[22] Over the last twenty-five years, catheter ablation techniques have become standard, curative therapy for AVNRT ,[17] accessory pathway ablation,[18, 20] and ablation of macro-reentrant atrial flutter.[19] While ablation of the AV junction has long been accepted as a palliative treatment for AF, curative catheter-based therapy has evolved rapidly since the early 1990s. Initial work focused on linear and MAZE-like lesions sets in the right,[23, 24] right and left,[25] and left atria.[26] More recently, the importance of AF triggers (particularly those located in the PVs) has been recognized and targeted. [27]

The Past

Initial ablation attempts to cure atrial fibrillation focused on linear lesions confined to the right atrium. Between 1994 and 1996, Haissaguerre and colleagues investigated the effects of linear lesion sets in patients with symptomatic, drug-refractory AF.[25] 45 initial patients were studied and followed over the long term. Patients initially underwent right atrial ablation only, with either a single ablation line from SVC to IVC over the atrial septum, or multiple lines (longitudinal and transverse) to compartmentalize the right atrium. The procedure led to stable sinus rhythm in 18 of 45 patients (40%) during the procedure. Sustained AF was inducible in 40 of 45 patients, however, and 19 patients underwent repeat ablation of left or right sided atrial flutter or focal atrial tachycardia. After a follow-up period of 11 ± 4 months, only 6 patients were free of AF off anti-arrhythmic drugs, with another 9 patients free of AF on a previously ineffective medication (overall success of 33%). 9 of 45 patients had significant improvement of their symptom burden with the aid of an anti-arrhythmic medication, while the remaining 21 of 45 patients had no appreciable effect from RA-only ablation. After 26 ± 5 months of follow-up,[24] there was a further reduction in therapeutic benefit, with 7 previous responders (either cure or significant reduction in AF burden) reverting to frequent AF. Successful results with RA-only lesions were seen in only 17 of 45 patients.

Other investigators have prospectively attempted curative lesion sets confined to the right atrium. Natale and colleagues studied 18 patients with symptomatic, drug-refractory AF.[28] While the lesion sets varied somewhat among the patients (seven with two intercaval lesions, ablation of the cavo-tricuspid isthmus, and an anterior RA line; eleven with a single intercaval line, a septal line, and cavo-tricuspid isthmus ablation), the results were generally poor. After a follow-up period of 22 ± 11 months, only 5 of 18 patients remained free from atrial arrhythmia recurrence. Most of the 13 recurrences occurred within two months of the procedure. The particular lesion set did not predict procedure efficacy. Thus, while linear ablation confined to the right atrium to cure AF is attractive from a technical and safety standpoint, multiple trials with intermediate and long-term follow-up have shown it to be a largely ineffective procedure.[24, 29]

Recognizing the limited efficacy of RA-only ablation for AF, several groups began prospective investigations of bi-atrial and left-atrial linear ablation. Haissaguerre performed left atrial ablation in 10 of their 45 patients described above .[25] Linear

ablation in this group terminated AF during the procedure in 8 of 10 patients. In 5 of 10 patients, sustained AF could not be induced after the procedure. Intermediate follow-up demonstrated success in 6 of 10 patients (with two patients requiring ongoing anti-arrhythmic medications).

Between 1996 and 1998, the same group systematically studied bi-atrial linear ablation to cure AF.[26] 44 patients were enrolled prospectively, the majority of whom suffered from paroxysmal, drug-refractory AF (n=40). 4 patients had persistent AF. All patients underwent a similar ablative procedure. In the right atrium, an intercaval septal line and ablation of the cavo-tricuspid isthmus were made. In the left atrium, linear lesions were applied from the superior PVs to the posterior MV annulus, including the inferior PV ostia. A roof line connecting the two superior PVs was performed in all patients; a septal left-sided line from the right superior PV to the fossa ovalis was performed in 23 of 44 patients.

This complex lesion set was technically difficult, requiring multiple procedures (2.7 ± 1.3) and prolonged fluoroscopy (171 ± 94 min).[26] After a follow-up period of 19 ± 7 months, 25 of the 44 patients were successfully treated, 12 patients were significantly improved, and 7 were without improvement. Success rates increased to 37 of 44 patients with the use of antiarrhythmic medications. However, there were clearly important caveats to the study. Only 7 of the patients were treated with a single procedure, while the rest were treated with multiple procedures for AF recurrence, ablation of AF triggers, and/or the ablation of iatrogenic left atrial flutters. Perhaps most importantly, triggers of AF arising from the PVs were identified and ablated in 26 of the 44 patients studied. Given the clear importance of trigger elimination in catheter-based cures of AF (discussed below), these results undoubtedly confounded an analysis of left atrial linear lesions alone as a curative approach to AF. Indeed, ablation of triggering foci and the creation of at least one successful line of block were the two sole predictors of success in the 37 patients with a favorable outcome.

Other linear left atrial lesion sets have been investigated. Swartz and colleagues pursued a catheter-based recreation of the Cox MAZE lesion set; technical difficulty and complication rates limited the widespread application of the procedure, however.[30] A much simpler left atrial lesion pattern was investigated prospectively by Pappone and colleagues.[31] 27 patients with highly symptomatic, drug-refractory, paroxysmal AF underwent biatrial lesion application using a novel (at the time) mapping system. 14 patients underwent biatrial ablation, with three linear lesions in the RA (posterior intercaval; cavo-tricuspid isthmus; septal) and a single, long linear lesion surrounding the PV ostia and connecting to the MV annulus in the left atrium. The left atrial lesion alone was performed in isolation in 5 patients, while the RA lesion set alone was performed in 8 patients. The success and complication rates reported by Pappone and colleagues were relatively good, with 16 of 27 patients entirely asymptomatic from AF (4 on antiarrhythmic medications), and another 4 with markedly reduced symptoms. No acute complications were reported. Success appeared to be predicted by biatrial ablation (85% success v. 50-60% with single-chamber ablation).

The Present

In part because of the limited efficacy of linear ablation alone for AF, and in part because of critically important observations by Haisaguerre of the triggered nature of AF (discussed below), linear ablation alone for AF is currently not widely performed. However, observations made by the groups that pursued linear ablation – unmasked triggering foci in patients undergoing linear ablation, and the development of simple lesion sets around the PV ostia, in particular – continue to inform current catheter-based ablation strategies for AF.

A seminal event in the catheter-based treatment of AF was the observation by Haissaguerre and colleagues that fibrillation could be triggered by rapidly firing ectopic atrial foci.[27,32,33] In a series of publications in the mid- and late-1990s, Haissaguerre's group reported the successful ablation of AF through radiofrequency ablation of focal trigger points. In 1994, they described three patients with atrial tachyarrhythmias.[32] In the first patient, a focal, rapidly firing atrial tachycardia mimicked AF on ECG, and was successfully ablated. The second patient had AT-induced AF, again with successful ablative therapy targeting the ectopic trig-

ger. In the final patient of the series, a focal right atrial septal trigger was found and ablated, with marked dimunition of AF burden. These initial results were expanded upon by a larger series of patients (n=9), in whom paroxysmal AF was found to be triggered from ectopic atrial foci.[33] In three patients, these foci were located in the RA; in the other six patients, triggers were at the ostium of the right (n=5) or left (n=1) PVs. All patients underwent successful ablation, with a mean of 4 ± 4 RF applications. One patient suffered an early recurrence of AF and underwent re-ablation. After 10 ± 10 months of follow-up, there were no observed recurrences of AT or AF.

In a larger, landmark study of 45 patients with symptomatic, drug-refractory paroxysmal AF, Haissaguerre et al reported that all 45 had demonstrable focal atrial triggers.[27] Most patients (n=29) had a single triggering site, although as many as four triggering sites were observed. A total of 69 triggering foci were found, the majority of which (31/69) were located in the left superior PV (LSPV). Other frequent sites included the right superior PV (RSPV; 17/69), left inferior PV (LIPV; 11/69), and right inferior PV (RIPV; 6/69). Three ectopic foci were located in the RA. AF induction was spontaneously observed in 36 patients, and was characterized by short bursts of two or more repetitive focal firings (40/45 patients). Ablation of ectopic foci was successfully achieved in 38/45 patients. Short-term recurrence of AF was seen in 2 of the 38 ablated patients. After 8 ± 6 months, 28 of the 45 patients remained free of AF (62%), without the use of anti-arrhythmic medications; 17 patients, including the early failures, had recurrence of AF.

The observation that AF is frequently triggered by ectopic, rapidly firing atrial foci amounted to a paradigm shift in ablative treatment. Surgical and catheter-based strategies to date had focused principally on substrate modification, in an effort to disrupt the maintenance of AF. Many of these strategies involved surgical or ablative isolation of the PV ostia from the body of the left atrium, which may in part explain their effectiveness. Current ablation strategies are focused more on the elimination and/or isolation of AF triggers, although many strategies combine both trigger isolation and substrate modification. Ablation of PV-located triggers has evolved rapidly, from focal to segmental and ultimately to linear ablation lesions.

With the initial observation that AF triggers are predominantly located in the PVs, focal trigger ablation within the veins became more widespread .[27,33-40] Quickly, though, the limitations and dangers of this strategy were discovered. The recurrence rates of AF in patients undergoing focal PV trigger ablation was high, due primarily to other PV triggers unrecognized at the time of initial ablation, or to recovery of identified and ablated PV triggers. As importantly, ablation within the PVs led to an unacceptably high rate of PV stenosis.[41,42] This complication has serious downstream sequella, including pulmonary hypertension, hemoptysis, dyspnea, and (rarely) death.[43] Accordingly, strategies to isolate the PVs, either through segmental or circumferential lesion sets, were developed in an effort to avoid injury to the PVs themselves.

Table 1. Summary of Clinical Studies of Segmental PV Ablation

			Success			Complications			
Study	Year	Follow-up (mo)	Overall	Paroxysmal AF	Persistent or Permanent AF	PV Stenosis (>50%)	Stroke	Cardiac Tamponade	Mitral Valve Injury
Haissaguerre et al[36]	2000	4 ± 5	51/70 (73)	51/70 (73)	–	0	0	0	0
Oral et al[40]	2002	5 ± 3	44/70 (63)	41/58 (71)	3/12 (25)	0	1 (1.4)	0	0
Deisenhofer et al[43]*	2003	8 ± 4	38/75 (51)	N/A	N/A	6 (8)	0	4 (53)	0
Marrouche et al[44]†	2003	14 ± 5	271/315 (86)	N/A	N/A	22 (7)	2 (0.6)	0	0
Arentz et al[45]	2003	12	34/55 (62)	26/37 (70)	8/18 (44)	1 (1.8)	0	1 (1.8)	0
Oral et al[47]	2003	6	27/40 (67)	27/40 (67)	–	0	0	0	0
Mansour et al[46]	2004	21 ± 5	22/40 (55)	19/33 (58)	3/7 (43)	0	0	2 (5)	0
Vasamreddy et al[42]	2004	11 ± 8	39/75 (52)	32/42 (76)	7/33 (21)	3 (4)	2 (2.6)	2 (2.6)	1 (1.3)
Overall	–	–	526/740 (71)	196/280 (70)	21/70 (30)	32 (4.3)	5 (0.7)	9 (1.2)	1 (0.1)

Values are given as n (%); success was defined as free of AF recurrence without antiarrhythmic drugs.
*Seven-day Holter monitoring was used to screen AF recurrence.
†Intracardiac echocardiography was used to monitor ablation in 259 patients.

Segmental PV isolation refers to the application of lesion arcs immediately outside the ostia of the PVs, and is based on the observation that discrete strands of myocardial tissue are found in PV ostia and represent attractive ablation targets. Segmental isolation is typically guided by a lasso catheter inserted into the PV, allowing for identification of the earliest activated region. A second ablation catheter is then used for lesion application. Ablation is performed at the region of earliest activation, with lesions placed outside the PV ostium.

Segmental ablation has been carefully studied in a number of prospective clinical trials (see Table 1]), [44] and remains a preferred method of some operators. Oral and colleagues investigated the efficacy of segmental ablation for patients with paroxysmal (n = 58) or persistent (n = 12) AF.[45] In all patients, at least three PVs were targeted (with variable inclusion of the RIPV), with 94% success in acute isolation. Patients were followed for 150 ± 85 days. There was a 70% cure rate (freedom from AF) and 83% clinical improvement rate (freedom from or marked reduction of symptomatic AF) in patients with paroxysmal AF. Those patients with persistent AF had markedly worse results, with only 22% of patients cured of AF. Subsequent data from this group demonstrated inferiority of their segmental approach to circumferential PV isolation (discussed below). A review of the compiled data evaluating segmental PV isolation demonstrates a combined efficacy that reflects the disparities in success rates seen between patients with paroxysmal and persistent AF described by Oral et al.[44] Intermediate-term success with segmental ablation was seen in 196 of 280 patients (70%) with paroxysmal AF, contrasted with 21 of 70 patients (30%) with persistent or permanent AF. PV stenosis remained a significant complication in these collected studies (incidence of 4.3%). Long term data in this group is limited.

Pappone and colleagues have championed an alternative strategy for PV isolation, in which large circumferential lesions are placed around the ostia of the PVs .[31,46-48] Several variations of the procedure are practiced: a single long lesion encompassing the ostia of all four PVs; twin lesions around the left and right PV ostia; or four lesions, each targeting a single PV. In each case, lesions are made empirically, rather than targeting particular regions of early PV activation. Success rates using wide, circumferential lesions have been favorable, typically ranging between 56 to 95%.[44]

Pappone and colleagues studied 251 patients consecutively between 1998 and 200049, employing the circumferential approach. The majority of their patients had symptomatic, drug-refractory paroxysmal AF (n = 179), though some patients had permanent AF (n = 72). In most cases, each PV was isolated individually, with circumferential lesions applied > 5mm outside the PV ostium. Some patients with closely paired or common PV ostia had larger lesions incorporating both ipsilateral PVs. The study reported follow-up data after 10 ± 4.5 months. In 179 patients with paroxysmal AF, 85% were free of AF; in 49 patients with per-

Table 1. Summary of Clinical Studies of Segmental PV Ablation

			Success			Complications			
Study	Year	Follow-up (mo)	Overall	Paroxysmal AF	Persistent or Permanent AF	PV Stenosis (>50%)	Stroke	Cardiac Tamponade	Mitral Valve Injury
Haissaguerre et al[36]	2000	4 ± 5	51/70 (73)	51/70 (73)	–	0	0	0	0
Oral et al[40]	2002	5 ± 3	44/70 (63)	41/58 (71)	3/12 (25)	0	1 (1.4)	0	0
Deisenhofer et al[43]*	2003	8 ± 4	38/75 (51)	N/A	N/A	6 (8)	0	4 (53)	0
Marrouche et al[44]†	2003	14 ± 5	271/315 (86)	N/A	N/A	22 (7)	2 (0.6)	0	0
Arentz et al[45]	2003	12	34/55 (62)	26/37 (70)	8/18 (44)	1 (1.8)	0	1 (1.8)	0
Oral et al[47]	2003	6	27/40 (67)	27/40 (67)	–	0	0	0	0
Mansour et al[46]	2004	21 ± 5	22/40 (55)	19/33 (58)	3/7 (43)	0	0	2 (5)	0
Vasamreddy et al[42]	2004	11 ± 8	39/75 (52)	32/42 (76)	7/33 (21)	3 (4)	2 (2.6)	2 (2.6)	1 (1.3)
Overall	–	–	526/740 (71)	196/280 (70)	21/70 (30)	32 (4.3)	5 (0.7)	9 (1.2)	1 (0.1)

Values are given as n (%); success was defined as free of AF recurrence without antiarrhythmic drugs.
*Seven-day Holter monitoring was used to screen AF recurrence.
†Intracardiac echocardiography was used to monitor ablation in 259 patients.

sistent or permanent AF, 68% were free of AF. Importantly, the procedure appeared to markedly reduce the incidence of PV stenosis (none), and was generally well tolerated (tamponade in 2 patients).

Oral and colleagues have directly compared the segmental and circumferential approaches in a randomized, prospective trial.[50] 80 patients, all with symptomatic paroxysmal AF, were evenly assigned to segmental or circumferential ablation. Ipsilateral veins were isolated in a single lesion with the circumferential technique. Procedure and fluoroscopy times did not vary significantly between the two groups. Success after 6 months, however, favored the circumferential (88% freedom from symptomatic AF) over the segmental approach (67% freedom from symptomatic AF). Complications did not vary meaningfully between the two groups, and were minimal (single iatrogenic LA flutter).

A recent review summarized the recent clinical trials investigating circumferential PV isolation efficacy (Table 2).[44] Long-term success was seen in 290 of 393 patients (74%) with paroxysmal AF. In patients with persistent or permanent AF, success rates were predictably lower (73 of 149 patients; 49%). Also predictably, the incidence of PV stenosis was markedly reduced compared to focal or segmental ablation (0.4%). Other complications, including tamponade, stroke, and death, were all under 1%. Based in large part on these trials, and on the aforementioned limitations of focal and segmental PV isolation, circumferential ablation around the PVs remains a commonly used technique, either alone or in conjunction with alternative approaches, in the catheter-based treatment of AF.

The Present - Johns Hopkin Hospital

At Johns Hopkins, we have prospectively investigated both segmental and circumferential techniques for AF ablation, publishing both intermediate- and long-term results.[51-55] We have chosen a stringent definition for success following AF ablation, defined as freedom from AF off all anti-arrhythmic drugs. An important consideration in evaluating clinical trials describing success rates in AF ablation is the often protean and changing definition of success (ranging from reduction of symptoms to elimination of the rhythm per se). Using the segmental approach to ablation in a series[51] of 75 patients with paroxysmal (n = 42), persistent (n = 21), or permanent (n = 12) AF, acute isolation of electrically active PVs was achieved in 100% of cases. 42 of 75 patients required isolation of all four PVs. After 10.5 ± 7.5 months following a single (n = 75) or second (n = 11) procedure, 39 of the 75 patients were free from AF, 10 of 75 patients were markedly improved, and 26 had no benefit from the procedure(s).

We prospectively investigated the circumferential approach in a series of 64 consecutive patients with paroxysmal (n = 29), or persistent/permanent (n = 35) AF. Patients were followed for a mean of 13 ± 1 months.[52] After a single procedure, long term success (freedom from AF) was found in 45% of patients. 19 patients with initial procedure failure elected to undergo a second procedure. The results including patients undergoing two procedures improved to an overall cure rate of 62%, with an additional 9% of patients significantly improved.

Based in part on these imperfect results, AF ablation techniques have continued to evolve at Johns Hopkins. Currently we perform a hybrid procedure that combines wide, circumferential ablation and limited segmental PV isolation. During this procedure, a double transseptal puncture is performed. PV electrical activity is monitored by lasso catheter. The right and left PVs are initially isolated in twin circumferential lesions. Following circumferential ablation, each vein is electrically isolated using a segmental approach, with care taken to avoid ablation in the PV itself. Long-term results from this procedure are forthcoming, and appear to be promising.

Finally, it is important to note that other centers have investigated extra-PV foci as targets for ablation, and have reported encouraging results. Nadamanee, for instance, has described ablation of atrial foci in which high-frequency atrial electrograms are recorded.[56] He found that these sites are typically located in 9 regions of the atria. Ablation during spontaneous or induced AF resulted in termination of fibrillation in 91% of cases, with a single-procedure success rate (freedom from AF off anti-arrhythmic medications) after 12 month

follow-up of 70%. Success increased to 83% after a re-do procedure.

The Future

There are several promising developments that may impact the near future of atrial fibrillation ablation. These principally include new technologies for lesion set delivery to the pulmonary vein ostia, consistent with current strategies targeting PV triggers. Focused ultrasound, cryoablation, and RF ablation catheters with customized lesion patterns for PV ostia are only some of the emerging technologies that may make PV isolation easier, faster, and safer. Other types of new therapies include the use of robotic ablation systems (Hansen Medical) and Stereotaxis.

It is difficult now to predict the future. However there are three possible strategies that will likely gain significant market share. One of these strategies involves the use of a balloon based ablation system (Focused Ultrasound, Cryoablation, or Laser). If one of these ablation systems gains market release and is shown to shorten procedure time and improve outcomes of AF ablation it is likely that many patients will initially undergo a balloon based ablation procedure. The obvious advantage of this approach is that expensive mapping systems are not required, making this therapy one that can be offered at virtually all hospitals that have based EP equipment. If an initial balloon based ablation procedure fails, or if a patient has long standing persistent AF they would be referred into a larger center with more sophisticated mapping equipment. A second strategy is the more widespread use of robotic or stereotactic ablation systems. If these systems are shown to improve outcomes and shorten procedure time it is possible that they would gain a very significant market share. The obvious advantage of these systems is that they provide the opportunity to automate much of the ablation procedure. And the third strategy that may remain dominant is the continued use of radiofrequency based ablation systems that heavily relay on electroanatomic mapping. At the present time, this latter approach is clear dominant.

It is clear that electrophysiologists are striving to find an ablation system or strategy that will deliver the best outcomes for their patients. At the present time all of the futuristic ablation systems described above are no more than promising possibilities. In order for these new ablation systems to gain widespread acceptance clinical trials will need to be performed which demonstrate increased efficacy, improved safety, and hopefully both shorter procedure times and reduced cost. Even if the first three are achieved, at an increased overall cost, this ablation system / approach will likely gain widespread acceptance.

In addition, there are ongoing trials looking at ablation versus anti-arrhythmic drug therapy for atrial fibrillation. While catheter ablation for AF is currently restricted primarily to patients with drug-refractory, highly symptomatic AF, a number of studies have investigated or are investigating ablation as a first-line therapy. The results of these trials may impact referral patterns for ablation in the near future.

Conclusions

Catheter-based therapies for AF have evolved rapidly over the last 15 years. One of the striking aspects of that evolutionary process has been the discovery of fundamental mechanisms underlying AF, often revealed during the course of clinical investigation. Triggering of AF from ectopic foci, atrial electrophysiological properties permitting arrhythmia maintenance, and the physical and electrophysiological remodeling that occurs in the setting of AF all have been elucidated, in large part, through clinical investigations.

As importantly, the efficacy and risk: benefit ratio of non-pharmacological interventions for AF continues to improve. New modalities of ablation, including ultrasound, laser, microwave, and cryoablation are all subjects of ongoing investigation. Given the rate of progress in AF therapy over the last quarter century, safer and more effective techniques seem certain to emerge over the next 25 years. Given the aging of the population, and the likely attendant flood of patients with AF at our doorstep, such advances are certainly worthy of aggressive pursuit.

References

1.Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG.

Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995; 155: 469-473.CrossRef Pubmed
2.Singer DE. Overview of the randomized trials to prevent stroke in atrial fibrillation. Ann Epidemiol. 1993; 3: 563-567.
3.Singer DE. Anticoagulation for atrial fibrillation: epidemiology informing a difficult clinical decision. Proc Assoc Am Physicians. 1996; 108: 29-36.
4. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 1991; 84: 527-539.
5.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: 1825-1833.
6. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002; 347: 1834-1840.CrossRef Pubmed
7. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med. 2000; 342: 913-920.CrossRef Pubmed
8.Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD,Jr, Raisch DW, Ezekowitz MD, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005; 352: 1861-1872. CrossRef Pubmed
9.Dogan A, Ergene O, Nazli C, Kinay O, Altinbas A, Ucarci Y, Ergene U, Ozaydin M, Gedikli O. Efficacy of propafenone for maintaining sinus rhythm in patients with recent onset or persistent atrial fibrillation after conversion: a randomized, placebo-controlled study. Acta Cardiol. 2004; 59: 255-261.CrossRef Pubmed
10.MOE GK, ABILDSKOV JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J. 1959; 58: 59-70.CrossRef Pubmed
11. MOE GK, RHEINBOLDT WC, ABILDSKOV JA. A COMPUTER MODEL OF ATRIAL FIBRILLATION. Am Heart J. 1964; 67: 200-220.CrossRef Pubmed
12. Moe GK. A conceptual model of atrial fibrillation.J Electrocardiol. 1968; 1: 145-146.
13. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. color:black'>A study in awake chronically instrumented goats. Circulation. 1995; 92: 1954-1968.
14.Allessie MA, Konings K, Kirchhof CJ, Wijffels M. Electrophysiologic mechanisms of perpetuation of atrial fibrillation. Am J Cardiol. 1996; 77: 10A-23A.
15. Allessie MA, Kirchhof CJ, Konings KT. Unravelling the electrical mysteries of atrial fibrillation. Eur Heart J. 1996; 17 Suppl C: 2-9.
16. Bhandari A, Morady F, Shen EN, Schwartz AB, Botvinick E, Scheinman MM. Catheter-induced His bundle ablation in a patient with reentrant tachycardia associated with a nodoventricular tract. J Am Coll Cardiol. 1984; 4: 611-616.
17. Lee MA, Morady F, Kadish A, Schamp DJ, Chin MC, Scheinman MM, Griffin JC, Lesh MD, Pederson D, Goldberger J. Catheter modification of the atrioventricular junction with radiofrequency energy for control of atrioventricular nodal reentry tachycardia. Circulation. 1991; 83: 827-835.
18. Calkins H, Sousa J, el-Atassi R, Rosenheck S, de Buitleir M, Kou WH, Kadish AH, Langberg JJ, Morady F. Diagnosis and cure of the Wolff-Parkinson-White syndrome or paroxysmal supraventricular tachycardias during a single electrophysiologic test. N Engl J Med. 1991; 324: 1612-1618.
19.Calkins H, Leon AR, Deam AG, Kalbfleisch SJ, Langberg JJ, Morady F. Catheter ablation of atrial flutter using radiofrequency energy. Am J Cardiol. 1994; 73: 353-356.CrossRef Pubmed
20.Jackman WM, Wang XZ, Friday KJ, Roman CA, Moulton KP, Beckman KJ, McClelland JH, Twidale N, Hazlitt HA, Prior MI. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. N Engl J Med. 1991; 324: 1605-1611.
21. Gaskell WH. On the Innervation of the Heart, with especial reference to the Heart of the Tortoise. J Physiol. 1883; -230.14.
22. Scheinman MM, Morady F, Hess DS, Gonzalez R. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. JAMA. 1982; 248: 851-855.CrossRef Pubmed
23. Haissaguerre M, Gencel L, Fischer B, Le Metayer P, Poquet F, Marcus FI, Clementy J. Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1994; 5: 1045-1052.CrossRef Pubmed
24.Jais P, Shah DC, Takahashi A, Hocini M, Haissaguerre M, Clementy J. Long-term follow-up after right atrial radiofrequency catheter treatment of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 1998; 21: 2533-2538.CrossRef Pubmed
25. Haissaguerre M, Jais P, Shah DC, Gencel L, Pradeau V, Garrigues S, Chouairi S, Hocini M, Le Metayer P, Roudaut R, Clementy J. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 1996; 7: 1132-1144.CrossRef Pubmed
26. Jais P, Shah DC, Haissaguerre M, Takahashi A, Lavergne T, Hocini M, Garrigue S, Barold SS, Le Metayer P, Clementy J. Efficacy and safety of septal and left-atrial linear ablation for atrial fibrillation. Am J Cardiol. 1999; 84: 139R-146R.Pubmed
27. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339: 659-666.CrossRef Pubmed
28. Natale A, Leonelli F, Beheiry S, Newby K, Pisano E, Potenza D, Rajkovich K, Wides B, Cromwell L, Tomassoni G. Catheter ablation approach on the right side only for paroxysmal atrial fibrillation therapy: long-term results. Pacing Clin Electrophysiol. 2000; 23: 224-233.CrossRef Pubmed
29.Gaita F, Riccardi R, Calo L, Scaglione M, Garberoglio L, Antolini R, Kirchner M, Lamberti F, Richiardi E. Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Electrophysiological findings and ablation results. Circulation. 1998; 97: 2136-2145.
30. Cox JL. Cardiac surgery for arrhythmias. J Cardiovasc Electrophysiol. 2004; 15: 250-262.CrossRef Pubmed
31. Pappone C, Oreto G, Lamberti F, Vicedomini G, Loricchio ML, Shpun S, Rillo M, Calabro MP, Conversano A, Ben-Haim SA, Cappato R, Chierchia S. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. Circulation. 1999; 100: 1203-1208.
32. Haissaguerre M, Marcus FI, Fischer B, Clementy J. Radiofrequency catheter ablation in unusual mechanisms of atrial fibrillation: report of three cases. J Cardiovasc Electrophysiol. 1994; 5: 743-751.CrossRef Pubmed
33. Jais P, Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, Clementy J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation. 1997; 95: 572-576.
34. Lau CP, Tse HF, Ayers GM. Defibrillation-guided radiofre-

quency ablation of atrial fibrillation secondary to an atrial focus. J Am Coll Cardiol. 1999; 33: 1217-1226.CrossRef Pubmed
35. Tsai CF, Chen SA, Tai CT, Chiou CW, Prakash VS, Yu WC, Hsieh MH, Ding YA, Chang MS. Bezold-Jarisch-like reflex during radiofrequency ablation of the pulmonary vein tissues in patients with paroxysmal focal atrial fibrillation. J Cardiovasc Electrophysiol. 1999; 10: 27-35.CrossRef Pubmed

36.Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation. 1999; 100: 1879-1886.
37. Lin WS, Prakash VS, Tai CT, Hsieh MH, Tsai CF, Yu WC, Lin YK, Ding YA, Chang MS, Chen SA. Pulmonary vein morphology in patients with paroxysmal atrial fibrillation initiated by ectopic beats originating from the pulmonary veins: implications for catheter ablation. Circulation. 2000; 101: 1274-1281.
38. Haissaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I, Garrigue S, Clementy J. Mapping-guided ablation of pulmonary veins to cure atrial fibrillation. Am J Cardiol. 2000; 86: 9K-19K.CrossRef
39. Haissaguerre M, Jais P, Shah DC Garrigue S, Takahashi A, Lavergne T, Hocini M, Peng JT, Roudaut R, Clementy J. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation. 2000; 101: 1409-1417.
40. Haissaguerre M, Jais P, Shah 12.0pt; DC, Arentz T, Kalusche D, Takahashi A, Garrigue S, Hocini M, Peng JT, Clementy J. Catheter ablation of chronic atrial fibrillation targeting the reinitiating triggers. J Cardiovasc Electrophysiol. 2000; 11: 2-10. CrossRef Pubmed
41. Saad EB, Marrouche NF, Saad CP, Ha E, Bash D, White RD, Rhodes J, Prieto L, Martin DO, Saliba WI, Schweikert RA, Natale A. Pulmonary vein stenosis after catheter ablation of atrial fibrillation: emergence of a new clinical syndrome. Ann Intern Med. 2003; 138: 634-638.
42. Saad EB, Rossillo A, Saad CP, Martin DO, Bhargava M, Erciyes D, Bash D, Williams-Andrews M, Beheiry S, Marrouche NF, Adams J, Pisano E, Fanelli R, Potenza D, Raviele A, Bonso A, Themistoclakis S, Brachmann J, Saliba WI, Schweikert RA, Natale A. Pulmonary vein stenosis after radiofrequency ablation of atrial fibrillation: functional characterization, evolution, and influence of the ablation strategy. Circulation. 2003; 108: 3102-3107.CrossRef Pubmed
43. Nilsson B, Chen X, Pehrson S, Jensen HL, Sondergaard L, Helvind M, Andersen LW, Svendsen JH. Acute fatal pulmonary vein occlusion after catheter ablation of atrial fibrillation. J Interv Card Electrophysiol. 2004; 11: 127-130.CrossRef Pubmed
44. Marine JE, Dong J, Calkins H. Catheter ablation therapy for atrial fibrillation. Prog Cardiovasc Dis. 2005; 48: 178-192.CrossRef Pubmed
45. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F,Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation. 2002; 105: 1077-1081.CrossRef Pubmed
46. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. Circulation. 2000; 102: 2619-2628.
47.Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Vicedomini G. Prospects of the treatment of atrial fibrillation. Circumferential radiofrequency ablation of pulmonary vein ostia. Recenti Prog Med. 2001; 92: 508-512.
48. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol. 2003; 42: 185-197.CrossRef Pubmed
49. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro MP, Mazzone P, Ficarra E, Di Gioia C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation. 2001; 104: 2539-2544.CrossRef Pubmed
50.Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, Veerareddy S, Pelosi F,Jr, Morady F. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation. 2003; 108: 2355-2360.CrossRef Pubmed
51. Vasamreddy CR, Lickfett L, Jayam VK, Nasir K, Bradley DJ, Eldadah Z, Dickfeld T, Berger R, Calkins H. Predictors of recurrence following catheter ablation of atrial fibrillation using an irrigated-tip ablation catheter. J Cardiovasc Electrophysiol. 2004; 15: 692-697.CrossRef Pubmed
52.Vasamreddy CR, Dalal D, Eldadah Z, Dickfeld T, Jayam VK, Henrickson C, Meininger G, Dong J, Lickfett L, Berger R, Calkins H. Safety and efficacy of circumferential pulmonary vein catheter ablation of atrial fibrillation. Heart Rhythm. 2005; 2: 42-48.
53. Vasamreddy CR, Dalal D, Dong J, Cheng A, Spragg D, Lamiy SZ, Meininger G, Henrikson CA, Marine JE, Berger R, Calkins H. Symptomatic and asymptomatic atrial fibrillation in patients undergoing radiofrequency catheter ablation. J Cardiovasc Electrophysiol. 2006; 17: 134-139.
54. Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J,Henrikson Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. J Interv Card Electrophysiol. 2006; 15: 145-155.CrossRef Pubmed
55.Cheema A, Dong J, Dalal D, Vasamreddy CR, Marine JE, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H. Long-term safety and efficacy of circumferential ablation with pulmonary vein isolation. J Cardiovasc Electrophysiol. 2006; 17: 1080-1085.CrossRef Pubmed
56. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004; 43: 2044-2053.CrossRef Pubmed