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Meet The Expert Doctor

Dr. Yaariv Khaykin,
MD, Ph.D
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Laser Ablation Of Atrial Fibrillation: Mid-term Clinical Experience

Li Poa, MD, Miguel Puig, MD, Pablo Zubiate, MD, Edward Ranzenbach, PAC, Shari-Knutson Miller, PAC, Christina Poa, PC, Hyunah Poa, MD

Cardiac Surgery, Enloe Heart Program, Enloe Medical Center, Chico, California, USA

Abstract

Background: Atrial Fibrillation is known to account for one third of all the strokes caused in the US in the population above the age of 70. Patients treated with the surgical Cox MAZE operation have been shown to have a 150 fold decrease in the incidence of stroke over an 18 year period. However, the original Cox MAZE although extremely successful in treating atrial fibrillation and decreasing the incidence of strokes was not performed widely because of complexity and invasiveness of the procedure. A variety of alternative energy based curative ablation strategies are now available for more minimally invasive therapeutic management of atrial fibrillation (AF). In this communication, we report our clinical experience in AF therapy utilizing laser energy ablation technology.

Methods: Fifty two consecutive AF patients underwent concomitant or isolated ablation prior to any coexisting cardiac procedures that included CAGB (coronary artery bypass surgery, MV (mitral valve) or AV (aortic valve) repairs. All patients had an epicardially based ablation pattern with basic lesions being en bloc type pulmonary vein isolation which included the antral surface of the left atrium, directed ganglionectomies of the the right anterior and inferior ganglions, posteriomedial ablation of the IVC (inferior vena cava), and a right isthmus ablation. Twenty seven patients had ligation of their left atrial appendage, 14 patients had resection of the ligament of Marshall, and three patients had endocardial placed lesions of a mitral annular connecting type lesion. In order to maintain the patients in normal sinus rhythm (NSR), electrical cardioversion and anti-arrhythmic drugs were employed as required.

Results: At a median follow-up of 250 days, 44 of the total 52 patients (84.6%) exhibited NSR.. No complications or mortality were reported due to the laser procedure.

Conclusion: Laser ablation was successfully and safely used for endocardial and epicardial AF ablation concomitant to other cardiovascular procedures and in the lone atrial fibrillation treatment utilizing a two port thoracoscopic approach.

Introduction

The operative success rate of the classical Cox-Maze procedure remains unparalleled when compared to other surgical options available to cure AF [Cox, 2000]. Critical challenge still persists in surgical practice when AF has to be treated concomitantly with co-existing cardiovascular problems [Melo, 1997]. Under these situations, Cox’s scalp based Maze procedure substantially elevates operative complexity and mortality. Due to these concomitant surgical “risks”, a number of alternative strategies utilizing energy sources viz., radiofrequency, microwave, and laser etc have
been developed and applied clinically [Lee 2001, Sie 2001].

Since December 2001, our clinical team has concentrated, more specifically, on employing microwave energy for therapeutic ablation of patients with AF and then since 2004 on laser energy as well. The purpose of this article was to evaluate the peri- and post-surgical outcomes for initial patients who underwent concomitant and isolated laser atrial ablation surgery.

**Methods**

**Patient Enrollment and Demographics**

Between November 2004 and June 2006, 52 consecutive permanent AF patients (38 men and 14 women; mean age: 68±12 years), who had an average left ventricular ejection fraction of 47 ± 15 %, underwent microwave ablation prior to concomitant open chest cardiac surgeries. The mean AF duration for our population set was 46 + 27 months. A summary of patient demographics is shown in table 1. Lone atrial fibrillation procedures utilizing a two port thoracoscopic access was performed in 21 patients. Combination procedures consisted of CABG in 16 patients, AV intervention in 9 patients, and MV intervention in 8 patients. The patients were classified with an average NYHA value of 3.125. A significant amount of our population, i.e. 65%, had congestive heart failure problems (n=34). Similarly, hypertension was recorded in 36 (69%) of our patients. All patients were consented through a formal IRB protocol.

**Pre-operative Management**

62% patients (32) were in pre-operative anti-arrhythmic drug therapy, 52% (n=27) employed β-blocking drugs, while 46% (n=24) of the patients utilized anti-coagulants. The average NYHA classification of the patients was 3.125. All patients had evaluations of their coronaries and cardiac valves prior to acceptance for lone AF treatment. Upon admission, baseline 12-lead electrocardiogram, basic chemistry panel 7, chest radiography and trans-thoracic echocardiography were performed. All patients underwent transesophageal echocardiography the day prior to surgery or in the operating theater after the induction of anesthesia to exclude the presence of left atrial thrombus. Patients were ordinarily diuresed twenty four hours prior to surgery to facilitate right atrial de-

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<table>
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<th>Men/Women, (n)</th>
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<tr>
<td>Age, yrs</td>
<td>68± 12, yrs</td>
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<tr>
<td>LA Diameter, mm</td>
<td>3.8+2.1, mm</td>
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<tr>
<td>Duration of AF, months</td>
<td>46 + 27, months</td>
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<tr>
<td>NYHA Class</td>
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<td>LV EF%</td>
<td>47±15%</td>
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**Table 1** | Patient demographics and success rates in the overall group, the lone AF group, and the overall concomitant cardiac intervention group

<table>
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<th>Patient Population</th>
<th>NSR (Success Rate)</th>
<th>AF</th>
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<tbody>
<tr>
<td>Total Population</td>
<td>52</td>
<td>44 (84.6%)</td>
</tr>
<tr>
<td>Lone AF Group</td>
<td>21</td>
<td>18 (86%)</td>
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<tr>
<td>Concomitant Group</td>
<td>31</td>
<td>26 (84%)</td>
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**Table 2** | Success rate in eradication of AF in the CABG, MV, and AV cases

<table>
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<th>Patient Population</th>
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<th>AF</th>
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<tbody>
<tr>
<td>CABG</td>
<td>16</td>
<td>14 (88%)</td>
</tr>
<tr>
<td>MV Cases</td>
<td>8</td>
<td>9 (89%)</td>
</tr>
<tr>
<td>AV Cases</td>
<td>7</td>
<td>9 (78%)</td>
</tr>
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compression in the scope type surgeries. Patients were also treated with perioperative steroids for twenty four hours to lessen the impact of inflammation in perioperative recurrence of atrial fibrillation.

**Operative Strategies**

Off-pump, epicardial ablation procedure was performed in all 52 patients and endocardially added lesions in 6 of the patients who were undergoing a mitral valve procedure. During these operations, the Encircle laser energy device (Edwards Lifesciences) was used for both epicardial and endocardial ablations. All of the patients had a basic lesion set of an epicardially based ablation pattern with basic lesions being en bloc box type pulmonary vein isolation which included the antral surface of the left atrium, directed ganglionectomies of the the right anterior and inferior ganglions, posteriomedial ablation of the IVC (inferior vena cava), and a right isthmus ablation. Care was taken to ensure that all lesions were closed loop lesions with no open end. These ablations consisted of direct application of laser energy to the ganglions as well as isthmus with the ganglions being clearly visible epicardial surface structures which is also demonstrated in the diagrams attached; directed ganglionic ablations in this manner have been seen in our practice to have improved our overall results over the prior 5 years. The ganglion ablations all demonstrated classic reflex bradycardia/tachycardia upon initiation of directed laser ablation which then resolved upon successful completion of ablation of the ganglionic plexus. Pulmonary vein isolation was tested with both entrance and exit block testing after ablation. Entrance block was demonstrated with a two electrode sensing catheter placed both inside and outside the pulmonary vein isolation box demonstrating more than a five fold differential in measured potentials and at least a 200 ms conduction delay. Exit block testing was performed with a pacing catheter placed within the isolation box at 10 joules of energy. Entrance block was obtained on all patients demonstrating successful completion of the pulmonary vein isolation; however, exit block could only be successfully confirmed in 41 of the 52 patients even with repeat ablations. Twenty seven patients had ligation of their left atrial appendage performed when there was shown to be a low flow state and when the left atrial appendage was safely accessible for ligation. 14 patients had resection of the ligament of Marshall during the time of this study based on other centers’ proposals for the possibility of improved success rates but was not continued when this was not seen to be the case. Six patients had endocardially placed lesions of a mitral annular connecting

**Figure:** Diagrams of Ablation Pattern

Pulmonary Vein Box Isolation
Directed right anterior ganglion ablation on Crista Terminalis and connected to box lesion set

Directed Right Inferior Ganglion Ablation and Left Inferior Ganglion ablation with ablation line crossing the Coronary Isthmus and attaching to the original box lesion set

Abbreviations:
AF : Atrial Fibrillation
NSR : Normal Sinus Rhythm
CABG : Coronary Artery By-pass Grafting
MV : Mitral Valve
AV : Aortic Valve
SVC : Superior Vena Cava
IVC : Inferior Vena Cava
LAA : Left Atrial Appendage
PV : Pulmonary Veins
TV : Tricuspid Valve
EF : Ejection Fraction
RF : Radiofrequency
type lesion which were in patients who already had a left atriotomy for access to the mitral valve during the course of the procedure. The most effective lesion set encompasses the full en bloc box type pulmonary vein isolation, directed R and L ganglionectomies, directed partial isthmus ablation, and the addition of a mitral annular connecting type lesion. Unfortunately, the addition of a mitral annular connecting type lesion requires a more invasive approach of utilizing extracorporeal circulation and the opening of the left atrium whereas all of the other aforementioned base lesions can be done epicardially either in combination with other cardiac surgery or even with just two 1 cm. thoracoscopic incisions as in the case of lone atrial fibrillation surgery.

Post-Operative Medication

Patients were discharged on anti-arrhythmic drugs and anti-coagulants for a period of 2 months. The anti-arrhythmic drug administration was discontinued after 9 weeks in the case of documented stabilized NSR. One month after discontinuation of anti-arrhythmics, patients were then monitored with an event monitor for one month whereupon a decision was then made with regards to cessation of anticoagulant medication.

Post-Operative Patient Management and Followup

During the hospital stay all the patients were monitored with continuous electrocardiography. Electrical cardioversion was carried out in patients who failed spontaneously to convert to sinus rhythm at the end of the ablation procedure and in whom pharmacological cardioversion was unsuccessful.

Statistical Analysis

Within group comparisons among the variables were carried out using Student’s-t test analysis. Statistical significance was accepted at a p-value < 0.05.

Results

Our overall experience reports restoration of stable sinus rhythm in 44 out of 52 patients (84.6%), post-operatively, at a median follow-up of about 250 days. More specifically, of the 16 CAGB patients, 14 (88%) were free from AF. 8/9 (89%) MV intervention patients and 7 of 9 AV repair patients (78%) were successfully converted to NSR. 18 /21 (85%) of the lone AF patients were successfully converted to NSR long term. In looking at the additional individual lesions of LA appendage ligation, 23/27 patients were found in NSR; ligament of Marshall resection, 10/14 patients were in NSR; and all six of the mitral patients with mitral annular connecting lesions were in NSR. The patients in NSR were all taken off antiarrhythmics and had documented maintenance on NSR two months post cessation of antiarrhythmics utilizing a 21 day event monitor prior to being documented as successful treatment. Any occurrence of atrial fibrillation or flutter lasting more than 5 minutes in length was defined as failure of therapy. Five of the 52 patients developed atrial flutter within the first two months post procedure with three resolving either spontaneously or post cardioversion and two patients went on to require additional catheter intervention. There were no reports of occurrences of stroke or any in hospital complications in our patient population. We had two deaths in the epicardial ablation group which was not attributable to the laser ablation but to an end stage hepatic failure which occurred 3 weeks after multiple procedures including a cardio-myopathy resection, AVR, MVR, and TVR; and other complications of the concomitant surgeries being performed. Overall, the average post-operative length of stay was 2.8 days with 20 of the 21 lone AF patients having only a one day length of stay. Four patients from the epicardial group and three patients from the endocardial group were successfully electrically cardioverted on an outpatient basis after going back into AF postoperatively. Three of the patients had pacemakers implanted for managing bradycardia or sick sinus syndrome but these were all in the concomitant surgery group; none of the lone AF patients required pacer insertion. Three patients from the epicardial group had spontaneous conversion to NSR on medication.

Discussion

Atrial fibrillation is the most common sustained cardiac arrhythmic disorder that substantially elevates the risk of morbidity and related mortality
Cardiac ablation appears to be equivalent to endocardial ablation in terms of NSR restoration and is quite successful with the use of laser energy. This result further demonstrates the effectiveness of laser energy when applied epicardially off pump. To our knowledge microwave and laser energies are the only energy sources which are being routinely used to perform off pump epicardial ablation through small port accesses at the time of this study. Radiofrequency belt sources are now available for port access as well.

It was reported that the patients who underwent the Cox-Maze procedure showed a significant decrease in the secretion of atrial natriuretic peptide (ANP) [Yoshihara 1998]. Since the atrial appendage is the main source of ANP we elected to oversew the LAA instead of completely excising it.

Limitations

Although a base lesion set is performed in all patients of this series, many patients did have additional lesions performed as well as LAA ligation. The individual numbers do not provide enough data to be able to discriminate the various additional lesions and their enhancement of successful atrial fibrillation treatment. However, the primary purpose of this paper is not to discuss the various lesions sets but to merely demonstrate the ability of using laser energy to safely create the lesions.

The followup time is over a median of 250 days which is limited because of the time period that was able to be studied; this paper gives enough followup so as to demonstrate safety and short to midterm efficacy but does not provide long term efficacy data which will be followed up in the future.

Conclusion

Laser energy was successfully and safely used for endocardial and epicardial AF ablation concomitant to other cardiac surgeries. There was no difference between epicardial and endocardial ablation outcomes in terms of NSR restoration. Based on our own promising results and experiences of other, all patients with a history of AF who are presenting for surgical treatment of other cardiac diseases can benefit from laser therapy. To mini-
mize morbidity, after ruling out any LAA thrombosis, the off pump epicardial approach is recommended for most patients. Furthermore, based on the known stroke risks and quality of life impairment associated with AF, the laser ablation procedure should be extended to most of the patients with stand-alone AF.

References

Introduction

Atrial fibrillation is a disease that affects over 5 million people worldwide. People with atrial fibrillation have greatly higher risks of cerebrovascular embolic events and long-term cardiadcysfunction. Methods to treat atrial fibrillation have been attempted since 1989, but because of the invasiveness of the various procedures the availability to patients have been small in numbers. The significant focus for atrial fibrillation has been mapped out since 1994, and been found to be centered within the ostia of the pulmonary veins. Therefore attention has been focused more recently on performing simplified isolation patterns around the pulmonary vein ostia.
Since 2002, epicardial attempts to create a pulmonary vein isolation lesions have utilized both microwave and radiofrequency energy sources. The success rates of these therapies have been fairly good, but some variances among the different groups have lead to continued research into energy sources with greater predictability of penetration and therefore greater safety and hopefully less variability on long-term success rates. Laser therapy has been identified as a potentially more incisive penetrating energy source relatively unaffected by intervening fat and fluid interfaces. This abstract summarizes a safety and efficacy study looking at performing epicardially based lesions to completely electrically isolate the pulmonary veins from the rest of the heart using laser energy. Laser energy seems to be potentially the ideal energy source to lead into a minimally invasive surgical method for pulmonary vein isolation, which would then make this procedure available for the vast majority of patients afflicted by atrial fibrillation worldwide.

Materials and Methods

The large pig model was utilized for creation of these isolating lesions of the pulmonary veins. Midline sternotomies were performed in 6 large pigs (94 kg – 105 kg). Pericardium was carefully incised and careful dissection was performed to dissect free the superior vena cava inferiorly from the right superior pulmonary vein. Careful dissection was also made to free the inferior vena cava from the pericardial surface and superiorly from the right inferior pulmonary vein. Careful dissection of the hemiazygos vein was performed on all six pigs with actual transection of the hemiazygos vein in the first pig and then later dissection of the hemiazygos from the left atrial surface in the latter five pigs.

The Optimaze E360 Surgical Ablation Handpiece from Edwards Lifesciences was utilized, which is a 4 centimeter diffusing diode laser (980 nm). The diffusing tip of the laser contains scattering particles in a silicone matrix that directs the energy radially and perpendicular to the fiber direction. The 4-centimeter laser is contained within a 25-centimeter sheath, which can be placed in one dissection around the pulmonary veins and then allows for mere advancement of the laser within the sheath itself. The laser generates 12 watts of power output per centimeter with the E360 Handpiece. Laser energy heats the water molecules to 50 degrees Celsius causing permanent cell death in these areas and fibrotic scarring, thereby causing an electrically impenetrable lesion. Ninety second energy bursts were performed at each 4-centimeter interval as the laser tip was advanced within the Optimaze sheath after the sheath had been placed Circumferentially around the pulmonary veins along the base of the left atrium. Careful inspection of the laser sheath was made to ensure placement superior to the coronary sinus, lateral to the left atrial appendage, and under the hemiazygos vein.

Upon completion of a circumferential isolating lesion around the pulmonary veins, confirmation of immediate electrical isolation of the pulmonary veins was performed with pacing being attempted from the right and left superior pulmonary veins. Hemostasis was affirmed and sternotomy closure was performed with stainless steel wires, 2-0 Vicryl, and 3-0 Vicryl sutures. A 24 french silicone chest tube was inserted laterally into each pericardial space. Average surgical time was 1.7 hours.

All 6 pigs were explored via bilateral thoracotomies at 40 days post ablation. Gross examination of the heart and left atrial contractility was performed and then sensing/recording electrodes were placed at the right atrial appendage, left ventricular anterior surface, and left atrial appendage. Pacing electrodes were placed on the surfaces of the right and left superior pulmonary veins. Pacing electrodes were then placed on the left atrialappendage to investigate the electrical competence of the left atrium. All pigs were then sacrificed with removal of the hearts and preservation in Prefer fixative. Pathologic gross examinations were performed of the hearts in general, and also specific histological examination of the ablation lesions in 6 different areas as well as examination for any potential abnormalities was performed.

Results

All six animals tolerated the ablation surgery well with appropriate weight gain post procedure over the ensuing 40 days in normal growth patterns. Careful gross examination was performed and there were no intra-operative complications noted during the ablation surgery such as coronary ar-
Table 1

Table 1: Pathological Findings

CS = Across or overlying the coronary sinus (posterior and inferior to the left pulmonary veins)
L = Lateral to the left pulmonary veins
P = Posterior left atrium (approx. midway between the left and right pulm. veins)
A = Anterior/superior left atrium (approx. midway between the left and right pulm. veins).

The specific findings for each of the pig hearts are presented below. Data include location and number of sections or slides examined, and the maximum dimensions of lesions identified in any (but not necessarily all) of the sections examined for that location. Lesions were measured along the endocardial surface, maximal width within the atrial myocardial wall, and thickness of transmural lesion extending from endocardium to epicardial connective tissue.

PIG # 391

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<td>5 mm</td>
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<td>L:</td>
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<td>A:</td>
<td>1</td>
<td>2 mm</td>
<td>8 mm</td>
<td>5 mm</td>
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NOTES: There was a 3-4 mm slightly dark spot on a mitral valve leaflet. Sections showed a few superficial telangiectatic vessels and a nearby small lymphoid aggregate, but no evidence of fibrosisor necrosis.

PIG # 404

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<td>A:</td>
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<td>7 mm</td>
<td>7 mm</td>
<td>3 mm</td>
</tr>
</tbody>
</table>

NOTES: There was a 5 mm dark thrombus identified within a vessel, close to but distinct from the coronary sinus. Sections show a vessel in the epicardial region with very recent clot (intact RBC membranes and no organization) within the lumen and some surrounding Masson’s lesion (papillary angioendotheliomatosis / organizing clot) in the surrounding connective tissue. Coronary sinus showed no thrombosis.

PIG # 405

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PIG # 406

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PIG # 407

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tery injury, pulmonary vein injury, coronary sinus injury, or left atrial perforation. Pulmonary vein isolation was confirmed in all six pigs utilizing the aforementioned methods of pacing from the right and left superior pulmonary veins and sensing from the skin place EKG electrodes.

Upon performing the redo surgery, one pig developed ventricular fibrillation with the resection of adhesions and could not be recovered. This expiration was directly related to the redo dissection and had no relationship to the ablation surgery itself. However, this pig could not then be tested for continued electrical isolation but did have the additional pathological examinations. All five remaining pigs were fully tested and demonstrated complete electrical isolation. Competent left atrial electrical conduction was demonstrated in all five pigs and good left atrial function was grossly identified in all six pigs. No gross evidence of cardiac injury was noted upon this exploration in all six pigs.

Gross pathology revealed all six heart specimens to be completely intact with no evidence of thrombus in any of the heart cavities, coronary sinus, coronary arteries, or pulmonary veins. The immediate gross examination revealed intact well defined ablation lesions with an otherwise completely normal cardiac structure. All chronic lesions had undergone a fibrotic change with occasional inflammatory residual changes at the borders of the fibrotic field. All lesions were fully transmural at each histologic sectioned point. Average depth of lesion for transmurality was 4 mm (range 3 mm – 7 mm) and average width of lesion was 7 mm (range 4 mm – 16 mm) (See table 1). The lesions were all well defined between scar zone and normal myocardial tissue. There was neither evidence of necrosis of endocardial tissue nor any evidence of thrombus material associated with any of the scar lesions. All lesions were close in proximity to the coronary sinus but the coronary sinus structure was noted to be patent without thrombus in all specimens.

One pigs’ mitral valve had a pigmented spot on the posterior leaflet which was separately sectioned and inspected to assure that this was just a pigmented spot and not an inadvertent injury to the valvular structure; all other valves were completely normal in the other 5 pigs.

**Comment**

Laser technology in the form of the E360 hand piece is able to reliably and consistently produce a well-defined electrical isolation scar around the pulmonary veins with minimal dissection with complete isolation block and complete safety. This technology should be able to successfully and safely treat all atrial fibrillation patients whose primary focus originates in the pulmonary veins. The most exciting aspect of this epicardial therapy with the E360 hand piece is its’ amenability to minimally invasive approaches to place the probe and there by perform the ablation surgery in solitary atrial fibrillation patients without an actual sternotomy.

**Disclosure and Freedom of Investigation**

The above protocol complied with the 1996 “Guide for the Care and Use of Laboratory Animals and was performed at the Edwards Lifesciences Biological Resource Center. One Edwards Way, M/S#PRT44 Irvine, CA 92614. For additional information contact: Jane M. Olin, DVM, Diplomat ACLAM 949-250-3508. All funding and testing equipment was provided by Edwards Lifesciences at no cost to the authors. All authors had full control of the design of the study, methods used, outcome parameters, analysis of data and production of the written report.

**References**

Cost-Effectiveness Of Catheter Ablation Treatment For Patients With Symptomatic Atrial Fibrillation

Nathalie Eckard1, Thomas Davidson1, Håkan Walfridsson3, Lars-Åke Levin1

1Center for Medical Technology Assessment (CMT), Department of Medical and Health Sciences, Linköping University, Sweden. 3Department of Cardiology, Linköping University Hospital, Sweden.

Abstract

Background: Atrial Fibrillation is the most common cardiac arrhythmia. It increases the risk of thromboembolic events and many atrial fibrillation patients suffer quality of life impairment due to disturbed heart rhythm. Pulmonary vein isolation using radiofrequency catheter ablation treatment is aimed at maintaining sinus rhythm ultimately improving quality of life. Randomized clinical trial have shown that catheter ablation is more effective than antiarrhythmic drugs for the treatment of atrial fibrillation, but its impact on quality of life and cost-effectiveness has not been widely studied.

Aims: To assess the cost-effectiveness of radiofrequency ablation (RFA) vs. antiarrhythmic drug (AAD) treatment, among symptomatic atrial fibrillation patients not previously responding to AAD.

Methods: A decision-analytic Markov model was developed to assess costs and health outcomes in terms of quality adjusted life years (QALYs) of RFA and AAD over a lifetime time horizon. We conducted a literature search and used data from several sources as input variables of the model. One-year rates of atrial fibrillation with RFA and AAD, respectively, were available from published randomized clinical trials. Other data sources were published papers and register data.

Results: The RFA treatment strategy was associated with reduced costs and an incremental gain in QALYs compared to the AAD treatment strategy. The results were sensitive to whether long-term quality of life improvement is maintained for the RFA treatment strategy and the risk of stroke in the different atrial fibrillation health states.

Conclusion: This study shows that the short-term improvement in atrial fibrillation associated with RFA is likely to lead to long-term quality of life improvement and lower costs indicating that RFA is cost-effective compared to AAD.

Key words: Cost, cost-effectiveness, decision-analytic model, ablation, atrial fibrillation, cardiovascular disease.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and occurs in 2% of adults aged 65 to 75 years. Its prevalence increases with age; 5% of adults above 75 years old and 14% of adults above 85 years old. Furthermore, AF increases the risk of thromboembolic events and many AF patients perceive/suffer quality of life (QoL) impairment in the form of palpitations and short-
ness of breath due to the disturbed heart rhythm. Pulmonary vein isolation using radiofrequency catheter ablation (RFA) is aimed at maintaining sinus rhythm. Randomized clinical trials have shown that RFA is more effective than antiarrhythmic drug treatment (AAD) in maintaining sinus rhythm, but its cost-effectiveness has not been widely studied. Cost comparison studies of RFA versus AAD were identified. Though, we could only identify two studies assessing both costs and benefits (effects) of RFA treatment.

Medical management for AF involves the use of a combination of different medications. Rhythm control management often involves the use of AAD, foremost amiodarone or flecainide, aimed at maintaining sinus rhythm and at avoiding relapses. Sotalol and propafenone are less commonly used for rhythm control management in Sweden. Many AF patients do not tolerate long-term AAD treatment, particularly with amiodarone, without side effects. In the event of side effects or lack of efficacy the use of a non-pharmaceutical treatment, such as pacemaker implantation followed by AV-node ablation or RFA might be considered. RFA is already an established treatment strategy for different types of arrhythmias including WPW-syndrome, AV-nodal reentry tachycardia, atrial flutter and focal atrial tachycardia. However, RFA, aiming at pulmonary vein isolation, for AF patients has only been used during the last decade and is usually considered as an alternative treatment strategy only after medical management has caused side effects or had no or insufficient effect.

AF has traditionally been divided into paroxysmal, persistent and permanent AF. According to international ACC/AHA/ESC 2006 guidelines patients with severe symptomatic paroxysmal and persistent AF are eligible for RFA treatment. The RFA treatment strategy for the treatment of symptomatic AF has been debated in the current Swedish National Guidelines for Heart Disease and is now recommended for symptomatic AF patients with paroxysmal or persistent AF not responding well to AAD treatment. Patients with permanent AF, on the other hand are not eligible for RFA and are excluded in the analysis.

In this analysis, we assess the lifetime costs and health outcomes of radiofrequency ablation (RFA) treatment compared to antiarrhythmic drug treatment (AAD) alone. The population used in our analysis consists of symptomatic patients with paroxysmal or persistent AF, not responding well to AAD treatment and eligible for RFA i.e. as a second-line treatment strategy.

**Methods**

**Overall analytical approach**

A decision-analytic model was developed to estimate costs, health outcomes and incremental cost-effectiveness of RFA compared to AAD treatment for AF for a lifetime time horizon. In the absence of long-term data, decision-analytic models can be used to estimate costs and health outcomes of health interventions beyond the follow-up of clinical trials. Data from several sources were used to populate the model with best available evidence. The outcome measure used in the analysis was quality-adjusted life years (QALYs). Probability distributions were defined for the model parameters reflecting the uncertainty in evidence/or the information available. A Swedish societal perspective was taken, and both costs and health outcomes were discounted at 3 % per annum, respectively. All costs are in 2006 prices and have been converted to USD using purchasing power parities (PPPs).

**Model structure and underlying assumptions**

A two-part model structure was used, a decision tree for the initial year in which the RFA procedure is assumed to take place, and a long-term Markov structure for subsequent years (see Figures 1a and 1b). The short-term model provides the proportion of patients entering the long-term model health states after accounting for non-stroke mortality and stroke risk. Short-term clinical endpoints i.e. freedom of AF at 12 months were used in the model. If the patient suffers a clinically significant relapse into AF, a second RFA procedure is usually offered as a standard in Sweden and was assumed to take place during the initial year.

A Markov model structure was developed to extrapolate the lifetime costs and QALYs of the two intervention strategies. In a Markov structure a hypothetical cohort of patients reside in mutually exclusive health states during intervals of equal length referred to as Markov cycles. The model
consists of health states for controlled AF, uncontrolled AF, stroke and death. Separate health states for death were used; whether caused by stroke or other cause mortality. Annual Markov cycles were applied.

Successful treatment implies that the hypothetical patients enter the controlled AF health state. If the treatment strategy is not successful, the cohort of patients enters the uncontrolled AF health state. In case of a stroke event, the cohort may enter the stroke dead or post stroke health states. The ‘post stroke’ health state implying an elevated mortality risk and reduced QoL. Patients face a risk of non-stroke mortality and may at any stage make the transition to the non-stroke dead health state.

**Figure 1A:** Short-term model structure.
A summary of base-case model inputs are given in Table 1.

**Model inputs**

**Clinical effectiveness**

We conducted a literature search to find data to populate our model. Clinical studies have shown a success rate for RFA, measured as freedom from AF relapses at 12 months, between 70 to 80 %, assuming that the intervention is repeated within a year in case of clinically significant relapse into AF or atrial tachycardia. Five randomized controlled clinical trials reporting efficacy of RFA compared with AAD were identified. One study was excluded as it only considered RFA as first-line treatment i.e. the patients did not receive AAD treatment prior to RFA. One of the randomized clinical trials found showing 56 % free from AF relapses during a follow-up period of 12 months of RFA treatment after a single procedure i.e. not repeated if failed. After a follow-up period of 12 months, 91 % (63/69) patients still using AAD had at least one AF recurrence with the AAD treatment strategy.

The probability used for the decision-tree was based on the assumption that the intervention is repeated within the first year in case of relapse into AF, the standard procedure in Sweden. The yearly rate of AF and relative risk ratios for both a first and a second RFA procedure were estimated using randomized controlled clinical trial data. An average of 1.4 procedures per patient is needed to successfully isolate the pulmonary veins based on Swedish clinical data.

**Mortality and stroke risks**

All AF patients with at least one risk factor for stroke (CHADS2) benefit from anticoagulation treatment to reduce thromboembolic events. No evidence was found to indicate different stroke risks in the controlled AF and uncontrolled AF health states. The baseline risk of stroke was assumed to be 1.5 % for AF and non-AF on anticoagulation treatment using a conservative assumption. The age-dependant standard mortality rates were based on the Swedish national data.

**Costs**

The short-term decision tree considered the costs associated with the RFA procedure. It was assumed that the RFA procedure was repeated with-
in a year if not successful implying an additional cost for the repeated procedure in the short-term decision tree. A single RFA procedure was costed at 90 000 SEK (9 860 USD).\textsuperscript{16-17} This cost includes 3 to 4 hospitalization days and diagnostic examinations e.g. ultrasound, CT /or MR and disposables such as catheters. This cost was thus Multiplied by 1.4 procedures in the Markov model.

Serious complications associated with the RFA procedure include; tamponade, bleeding, pulmonary vein stenosis, stroke and oesophageal fistulas.\textsuperscript{18} Deaths have been reported in some cases in connection with pulmonary vein stenosis and oesophageal fistulas. In the Swedish national catheter ablation register information on complications associated with RFA treatment was available. The probability of a major complication was assumed to be 3 % using Swedish register data, no deaths were reported.\textsuperscript{19} All complications used

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of model inputs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Value</td>
</tr>
<tr>
<td>Probability of AF free at 12 months</td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>0.780</td>
</tr>
<tr>
<td>AAD</td>
<td>0.090</td>
</tr>
<tr>
<td>Rate of AF in AAD</td>
<td>2.4423</td>
</tr>
<tr>
<td>Risk ratio RFA vs AAD</td>
<td>0.1017</td>
</tr>
<tr>
<td>Stroke risk, AF (%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke risk, free from AF (%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Complication with RFA</td>
<td>0.030</td>
</tr>
<tr>
<td>Cost items</td>
<td>Mean costs; SEK (USD)</td>
</tr>
<tr>
<td>RFA procedure, single event*</td>
<td>90 000 (9 860)</td>
</tr>
<tr>
<td>Complication cost</td>
<td>20 000 (2 190)</td>
</tr>
<tr>
<td>AAD treatment, annual</td>
<td>15 000 (1 640)</td>
</tr>
<tr>
<td>Anticoagulation treatment, annual§</td>
<td>7 000 (770)</td>
</tr>
<tr>
<td>Cost of stroke (yr 1)</td>
<td>175 000 (19 180)</td>
</tr>
<tr>
<td>Cost of stroke (&gt;yr 1, per annum))</td>
<td>40 000 (4 380)</td>
</tr>
<tr>
<td>QALY-weights for males in normal population Age</td>
<td>QALY-weights</td>
</tr>
<tr>
<td>&gt;69</td>
<td>0.830</td>
</tr>
<tr>
<td>70-79</td>
<td>0.800</td>
</tr>
<tr>
<td>80&lt;</td>
<td>0.740</td>
</tr>
<tr>
<td>Decrement for AF</td>
<td>0.100</td>
</tr>
<tr>
<td>Decrement for stroke</td>
<td>0.250</td>
</tr>
<tr>
<td>Annual discount rate</td>
<td>0.03</td>
</tr>
<tr>
<td>Costs</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Average cost for RFA procedure includes; 3-4 hospitalization days, diagnostic examinations e.g. ultrasound and/or CT and MR and catheters.
§ Anticoagulation treatment (warfarin) consists of; monitoring at specialist dept. (58 %), average cost per unit, 200SEK (22USD); number of visits per annum, 16.25; monitoring at primary care unit average cost per unit 545SEK (60USD) (42 % average cost 509SEK (56USD) of which 10 % at home, average cost 861SEK (94USD), number of visits, 13.75; travel, 42SEK (5USD); loss of production, 26SEK (3USD) and medication 576SEK (63USD).
in our model were treated as costs.

Medical management for AF often involves the use of a combination of different medications. Both the RFA and AAD treatment strategy involves the use of AAD. The annual cost of AAD treatment has been estimated to 15 000 SEK (1 640 USD). This cost includes hospitalisation, AAD medication and consultation; hospitalisation being the major cost driver for AAD. In the long-term model, continued use of AAD after the initial year, was assumed in the case RFA did not eliminate AF i.e. not free from AF.

The average cost of monitoring AF patients using warfarin (anticoagulation) was 375 SEK (41 USD) per visit and 15 times a year, totalling to 6 052 SEK (663 USD) per annum. This cost includes the cost for monitoring at either a specialist department or primary care unit and actual medication. The cost of medication was estimated to 575 SEK (63 USD) per annum. The post stroke health state is associated with increased cost and the annual cost of stroke was assumed to be greater during the first year, based on the incidence of first-time stroke.

Quality-adjusted life years

No studies were found measuring QoL improvement on AF patients in a way that could readily be used for QALY weights. However, several studies have shown improved quality of life (QoL) after RFA treatment. For instance, QoL, measured by the SF-36 instrument, improved significantly in all eight health dimensions after RFA treatment. In order to estimate QALY weights for different health states, age-adjusted QALY weights based on a Swedish general population were applied for patients in the controlled AF state, and used as reference points. The QALY weights used in the model was 0.83, 0.81 and 0.74 for individuals aged >69, 70-79 and >80. Decrement were applied to the general population utility weight for the uncontrolled AF state and the post stroke state. A decrement of 0.1 for uncontrolled AF and 0.25 for stroke was applied to the baseline utility in the controlled AF state.

Analysis

The model was evaluated using second-order Monte Carlo simulation. The cohort was simulat-

---

Table 2 | Quality adjusted life years and incremental cost effectiveness ratios for RFA compared with AAD treatment.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>QALY</th>
<th>Cost (USD)</th>
<th>ICER (USD)/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilistic base-case analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>9.46</td>
<td>232 300 (25 460)</td>
<td></td>
</tr>
<tr>
<td>AAD</td>
<td>8.68</td>
<td>277 700 (30 440)</td>
<td>Dom</td>
</tr>
<tr>
<td>Annual probability of reversion to uncontrolled AF after RFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 % RFA</td>
<td>9.06</td>
<td>318 600 (34 920)</td>
<td></td>
</tr>
<tr>
<td>AAD</td>
<td>8.55</td>
<td>279 700 (30 660)</td>
<td>75 500 (8 280)</td>
</tr>
<tr>
<td>10 % RFA</td>
<td>8.91</td>
<td>366 400 (40 160)</td>
<td></td>
</tr>
<tr>
<td>AAD</td>
<td>8.55</td>
<td>279 700 (30 660)</td>
<td>241 400 (26 460)</td>
</tr>
<tr>
<td>15 % RFA</td>
<td>8.81</td>
<td>395 300 (43 330)</td>
<td></td>
</tr>
<tr>
<td>AAD</td>
<td>8.55</td>
<td>279 700 (30 660)</td>
<td>440 800 (48 310)</td>
</tr>
</tbody>
</table>

ICER, Incremental cost-effectiveness ratio; QALY, quality adjusted life years; RFA, radiofrequency ablation treatment; AAD, antiarrhythmic drug treatment. Dom, dominant.
ed during Markov cycles until all hypothetical patients were assumed to be in the ‘dead’ health state during sixty-one Markov cycles. The total accumulated costs and health outcomes for each Markov cycle were summarized for the hypothetical cohort of symptomatic AF patients. The results were presented in two ways. First, mean lifetime costs and QALYs showing the incremental cost-effectiveness ratios (ICERs) of the compared treatment strategies are shown in Table 2 illustrating the additional costs needed per additional gained QALY. Second, decision uncertainty of the probabilistic analysis is plotted in the cost-effectiveness plane. The model was programmed and analyzed using Microsoft Office Excel.

Results

Base-case analysis

The base-case results show that the RFA treatment strategy was associated with an incremental gain in QALYs and reduced costs compared to the AAD strategy in the lifetime analysis. The model was run probabilistically and the results of the 1000 simulations are shown in Figure 2. The vertical axis represents the difference in costs and the horizontal axis the difference in health outcomes for the two treatment strategies. The plotted results imply that most of the ICERs are more effective and less costly in the SE quadrant and more costly in the NE quadrant. If the benefits of the RFA treatment strategy are sustained during a lifetime, the RFA treatment strategy would be the optimal one.

Alternative scenarios

One-way deterministic sensitivity analysis was performed to assess whether the results were affected by changes in the model assumptions. The results of the analysis are dependent whether the

Figure: 2 Cost-effectiveness plane of probabilistic base-case analysis of RFA vs. AAD.

Scatterplot diagram to illustrate uncertainty in the results of the analysis. Each point represents the result from one simulation run based on parameter values drawn from prespecified statistical distributions. Results measured in additional (incremental) costs and QALYs gained (incremental effects) by replacing AAD with RFA in the lifetime analysis. The SE quadrant implies a treatment strategy associated reduced costs and incremental gain in QALYs i.e. is considered a dominant treatment strategy.
long-term positive effect of RFA is maintained over a lifetime period i.e. patients remaining free from AF. In the absence of data beyond a 12 month follow-up period, we considered annual reversion rates back to uncontrolled AF after RFA of 5 %, 10 % and 15 % annually, in the alternative scenarios (Table 2). The results of the analyses were sensitive to reversion back into AF, implying both decreasing QALYs and higher costs for the RFA treatment strategy. Even though the results were sensitive to reversion back into AF, the costs of RFA are only slightly higher compared to the AAD treatment strategy. The benefits (QALYs) of RFA are always higher than that of the AAD strategy in the alternative scenarios. In spite of higher costs and decreasing QALYs for the RFA strategy, Table 2 is to be interpreted, by combining both costs and benefits in the ICER column. For all values tested, the ICERs were below the so called threshold value for what is considered cost-effective (ranging from dominant to 440 800 SEK (48 310 USD).

Little is known whether the elevated stroke risk in the AF health state is eliminated with the RFA treatment strategy. In the base-case analysis an estimate of 1.5 % was used for both controlled and uncontrolled AF. In the sensitivity analysis the stroke risk was varied in the uncontrolled AF health state. There are more patients in the AF state in the AAD treatment strategy. An elevated stroke risk for the AF state will decrease health outcomes in the AAD treatment strategy. As there are more AF patients in the AAD strategy, the AAD treatment strategy is disfavoured.

Discussion

Our results, based on a modelling approach, indicate that the RFA treatment strategy is cost-effective. We assessed lifetime costs and effects using relevant randomized controlled trials, different published papers and Swedish register data as input variables for both treatment strategies. Using probabilistic analysis allows uncertain parameters to vary randomly within predefined distributions reflecting the overall level of uncertainty of model parameters.

There are several sources of uncertainty to be considered when interpreting the results associated with methodological aspects and model assumptions. We used a lifetime time horizon to analyse the model. A lifetime time horizon is relevant, as benefits are likely to accrue well beyond the duration of a clinical trial and costs are largely the result of the initial intervention. The main costs for RFA treatment occurs during the first year due to considerably higher intervention costs compared to AAD treatment.

The RFA treatment strategy, when used as a second-line strategy, is the standard procedure in Sweden and in accordance with international guidelines. AAD treatment involves the daily use of medications and is not always well tolerated by the patient. This is also a reason why the RFA might be considered cost-effective compared to AAD. The AAD strategy has often proven non-successful and the low efficacy AAD therefore favours the RFA treatment strategy. One could argue that the AAD treatment strategy might be associated with a higher disutility compared to the RFA treatment strategy. We chose to use conservative estimates as not to disfavour the AAD treatment strategy in the base-case scenario.

The two key parameters we found to be most important to examine were the reversion rates of the RFA procedure back to AF and variations in stroke risks in the different AF health states. We found no long-term studies of the sustainability of the RFA treatment strategy i.e. if the QoL benefits are maintained over a lifetime period. We considered different annual reversion rates back to AF in the alternative scenarios, implying both decreasing QALYs and higher costs for the RFA strategy. Even though the results were sensitive to reversion back into AF, the costs of RFA are only slightly higher compared to the AAD treatment strategy. The benefits (QALYs) of RFA are always higher than that of the AAD strategy in the alternative scenarios. In spite of higher costs and decreasing QALYs for the RFA strategy, Table 2 is to be interpreted, by combining both costs and benefits in the ICER column. For all values tested, the ICERs were below the so called threshold value for what is considered cost-effective (ranging from dominant to 440 800 SEK (48 310 USD).

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Only two studies were found assessing cost-effectiveness of the RFA treatment strategy. 4-5 The US study concludes that RFA treatment is potentially cost-effective for symptomatic AF patients compared to medical management. The benefit of each treatment strategy was driven primarily by stroke risk reduction. A wide range of efficacy rates were explored and there is a risk that the effects of the RFA treatment strategy have been overestimated. Early studies have indicated that RFA is a curative treatment strategy and the US study
also refers to the restoration of sinus rhythm. We found no evidence to indicate stroke risk reduction in the controlled AF health state after an RFA procedure. The second study was based on a UK population using a similar model structure to ours. The UK study has considerably higher probabilities for the success rates for both the RFA and AAD treatment strategies compared to our study. The clinical effectiveness input variables in the UK study were based on a meta-analysis. It is unclear whether the high efficacy refers to a mix of first- and second-line treatment. There is also the possibility of bias toward one study with higher efficacy compared to other clinical studies. However, both previous cost-effectiveness studies are in line with our results, indicating a cost-effective treatment strategy for RFA if QoL improvement is maintained. Other studies were found comparing catheter ablation treatment with medical management but not in relation to effects. The cost comparison analyses by Khaykin et al. studied RFA versus AAD both as a second-line and first-line treatment strategy. They conclude that the RFA treatment strategy was considered cost-equivalent at 4 years when used as second-line treatment strategy and was cost neutral at 2 years when used as a first-line treatment strategy.

The results were sensitive to whether the long-term QoL benefits are maintained after the initial RFA procedure. Follow-up studies would be important when confirming the sustainability of the RFA treatment strategy. Our modelling approach provides an analytic framework and new parameter estimates can readily be incorporated into the model once more evidence becomes available.

In conclusion, the RFA treatment strategy was associated with reduced cost and an incremental gain in QALYs and was considered a cost-effective treatment strategy compared to the AAD in a lifetime perspective, despite higher initial intervention costs.

Acknowledgements

We would like to thank Martin Henriksson for valuable modeling support during the working process.

References

19 Swedish national catheter ablation register, 2007.


The Autonomic Nervous System and Atrial Fibrillation: The Roles of Pulmonary Vein Isolation and Ganglionated Plexi Ablation

Benjamin J. Scherlag, PhD, Hiroshi Nakagawa, M.D, Ph.D Eugene Patterson, PhD, Warren M. Jackman, MD, Ralph Lazzara, MD, Sunny S. Po, MD, PhD
Heart Rhythm Institute at the University of Oklahoma Health Sciences Center, Oklahoma City, OK

Abstract

After the sequential successes of catheter ablation for the treatment of pre-excitation syndromes (WPW), junctional reentry (AVNRT) atrial flutter (AFL) and ventricular arrhythmias, clinical electrophysiologists have focused on the myocardial basis of atrial fibrillation (AF). Thus, the strategy for ablation of drug and cardioversion refractory AF was to isolate the myocardial connections from the focal firing pulmonary veins (PVs) in addition to altering the atrial substrate maintaining AF. However, the overall success rates have not achieved those of the other types of ablation procedures. In this review we have summarized the favorable aspects and drawbacks of pulmonary vein isolation (PVI). As for the role of the Intrinsic Cardiac Autonomic Nervous System (ICANS), both basic and clinical evidence has shown that ganglionated plexi (GP) stimulation promotes initiation and maintenance of AF, and that GP ablation reduces recurrence of AF following catheter or surgical ablation of these structures. Based on these findings, the GP Hyperactivity Hypothesis has been proposed to explain, at least in part, the mechanistic basis for the focal form of AF. For example, PV isolation may not always be necessary for elimination of AF, as in the early stages of paroxysmal AF. GP ablation alone, in these cases, may suffice for focal AF termination. In the persistent and long standing persistent forms the substrate for AF may be more extensive and therefore require GP ablation plus PV isolation and/or CFAE ablations. Clinical reports, both catheter based as well as minimally invasive surgical procedures, which include PVI plus GP ablation have shown relatively long-term success rates much closer to or equal to those achieved by myocardial ablation procedures in patients with WPW, AVNRT and AFL.

Historical Background

Clinical Electrophysiology, a subspecialty of Cardiology, had its beginnings in the 1960s and 1970s with the development of new intra-cardiac electrical recordings techniques\(^1,2\) and procedures for provocative pacing of the atria and ventricles\(^3\). These diagnostic tools provided more precise insights as to the mechanisms of various cardiac arrhythmias\(^4-6\) than previously achieved by the use of the electrocardiogram alone. Another milestone occurred in 1981 with the use of atrioventricular (A-V) junctional ablation to control the rapid ventricular response in a patient with...
atrial fibrillation. The use of radiofrequency energy [8] became the mainstay for catheter ablation as a curative approach for a number of cardiac arrhythmias which were previously treated, most not effectively, by drugs.

Subsequently, Kuck et al [9] and Jackman et al. [10] used radiofrequency energy for catheter ablation of accessory pathways, and the A-V junction. These procedures were followed in rapid succession by radiofrequency ablation of the slow A-V nodal pathway to cure A-V junctional reentrant tachycardia [11, 12] and the ablation of the inferior vena cava-tricuspid valve isthmus to terminate atrial flutter. [13] The factor common to this non-surgical, non-pharmacological therapy was the use of radiofrequency lesions to interrupt a reentrant circuit which served as the substrate for these cardiac arrhythmias.

Based on the 95-99% success rates resulting from their previous successes, clinical electrophysiologists confronted the most common and most vexing of the cardiac arrhythmias, atrial fibrillation (AF). The initial attempts followed the success of the surgical Maze technique. [14] Instead of cut and sew, Swartz et al [15] used radiofrequency catheter ablation to induce bi-atrial linear lesion sets. Others, [16] using similar approaches in an attempt to mimic the surgical procedure but with the use of radio-frequency energy, had low success rates and unexpected complications.

A seminal discovery was made just before the turn of the century with the observation by the Bordeaux group, that patients with drug and cardioversion resistant paroxysmal AF consistently manifested focal firing arising from the myocardial sleeves of the pulmonary veins. [17, 18] This breakthrough observation represented a radical departure from the prevailing view that the mechanism responsible for AF was based on multiple reentrant wavelets continuously encircling the atria. [19, 20] Initially, the clinical strategy adopted was to locate the focal firing sites within the PV(s) and ablate them with radiofrequency current. [21] Although this strategy was effective in treating this form of AF, 62% success over the short term, several factors caused this approach to be abandoned: 1) The danger of PV stenosis, 2) The finding that all the PVs were potential arrhythmogenic sites and 3) In approximately 15% of this AF subpopulation non-PV focal firing sites could be identified. [22, 23]

**Pulmonary Vein Isolation (PVI)**

These factors engendered the strategy of PV isolation (PVI) which was undertaken to not only prevent the escape of the PV triggers [24] but also to markedly reduce the affected substrate maintaining AF. In regard to the latter, somewhat different procedures were devised including left atrial circumferential ablation [LACA, 25]; wide area circumferential ablation [WACA, 26]; and pulmonary vein antrum isolation [PVAI, 27]. All of these, performed as a single procedure, have resulted in success rates as high as 84% for paroxysmal and persistent AF [28] but relatively lower success rates for long standing persistent AF.

Another important catheter based technique for ablation of AF was reported by Nademanee et al [29] who specifically targeted sites showing low level complex fractionated atrial electrograms (CFAE) during AF. They reported, of the 121 patients treated, 110 (91%) patients were free of arrhythmia and symptoms, 92 (76%) after one procedure and an additional 18 after two procedures, with a follow-up of 1 year. More recent studies have combined techniques in order to increase success rates particularly in patients with long standing persistent forms of AF. In a recent study by Elayi et al [30] in 144 patient with long standing persistent AF, after a mean follow-up of 16 months, these investigators reported that a hybrid technique consisting of pulmonary vein antrum ablation (PVAI) plus ablation of CFAE provided a better outcome than either circumferential pulmonary vein ablation (CPVA) or PVAI with the highest success rates seen with the hybrid approach after 2 procedures (94%).

**Consequences of PVI**

The PVI procedure could require 100+ radiofrequency applications. [25] Even those procedures which targeted CFAE, [29] without PVI, as few as 40 or as many as 140 radiofrequency applications were delivered to achieve the ablation endpoint. A recent consensus statement reported serious complications in 6% of more than 8700 cases including cardiac tamponade, PV stenosis, phrenic nerve injury, esophageal injury/left atrial fistula, thromboembolism, among others. [28] Early on atrogenic con-
sequences were reported with PVI procedures in the form of recurrent tachyarrhythmias. The lesion sets induced to isolate PV firing by encircling lesion sets tend to establish a large channel which favors the induction of a macro-reentrant circuit and subsequent atrial tachycardias. In order to prevent such occurrences additional lesion sets were introduced: a left atrial roof line and a mitral isthmus line. More recently other procedures have been introduced as well, such as ablation of area showing CFAE and areas within the coronary sinus or within the superior vena cava. These additional lesion sets further increase the risk of gaps which in and of themselves provide channels that can allow macro-reentrant atrial tachycardias or left atrial flutters to develop. These recurrences have, therefore, necessitated repeat or even multiple procedures to close gaps and terminate the iatrogenically induced arrhythmias.

Once the ablation within or at the ostia of the PV was abandoned most centers adopted the circumferential approach proposed by Pappone et al. The rationale for the strategy of PVI was basically to isolate the rapid ectopic firing arising within or at the ostium of the PV without incurring, PV stenosis. However the results, albeit positive (70-80% success), were somewhat counter-intuitive. Pappone et al. found that “isolation of PV foci may not be the sole mechanism responsible for the AF cure, as suggested by our finding of no significant relationship between lesion completeness and clinical outcome… PV isolation might have interrupted pathways crucial in the genesis of AF located at the PV-LA junction…Finally, atrial debulking and/or denervation may have contributed to suppression of AF.” Subsequent studies further amplified the questions raised by Pappone et al. For example, Stabile et al., using the same anatomic approach with circumferential lesion sets, found that PVI

Figure 1: A diagrammatic representation of the neural network that extends over the right and left atria as well as on the epicardial surface of the ventricles. This illustration is the drawing taken from the publication by Pauza et al. showing the course of nerves which were seen after acetylcholinesterase staining. In this study, ganglia within fat pads are not depicted although as many as 4300 intrinsic neurons were estimated to be found in the adult human heart. (Reproduced by permission from Pauza et al. Anatomic Record 2000;259:353-382.)

was “not crucial in determining clinical success”.
Cappato et al found that, after the first procedure, clinical success was observed in “32% of patients despite the presence of late conduction

Figure: 2 View of the fat pads (panel A) on the human heart as seen through a right thorascopic port. The fat pads (which contain the anterior and inferior right GP) are shown within the demarcated areas (dashed lines) lying between the right superior and right inferior pulmonary veins (RSPV, RIPV). Panel B. A thorascopic view from a left sided port showing the left superior and left inferior, LSPV, LIPV as well as the ligament of Marshall (LOM). The superior left GP is located at the junction of the LSPV and the pulmonary artery while the left inferior GP is located inferior and posterior to the LIPV.
recurrence across the disconnecting line of one or both superior PVs ...in particular, 11 (79%) such patients had conduction recurrences in both superior PVs”. Cappato et al. state, “Causes accounting for this effect may include occasional ablation of the culprit arrhythmogenic focus and severe impairment of conductive PV tissue crucial for arrhythmia generation...” Whether such an explanation can be applied to other findings suggesting that clinical success of PVI electrical disconnection can also be achieved, at least for some time, despite conduction recurrence remains moot. Other possibilities that may account for these findings are presented below.

The Hyperactive GP Hypothesis: The PVI Paradox

Intrinsic Cardiac Autonomic Nervous System

The role of the intrinsic cardiac autonomic nervous system (ICANS) under physiological and pathological circumstances has been of interest for the past 40 years. To paraphrase Ardell the intrinsic neural network on the heart and within the pericardium, serves as more than a relay station for the extrinsic projections of the vago-autonomic system from the brain and spinal cord to the heart. It functions as an integrative system which acts cooperatively with the extrinsic innervations but can act independently to modulate numerous cardiac functions, e.g., automaticity, contractility, conduction etc. Early basic studies showed the relationship between the ICANS and cardiac arrhythmias.

Anatomy of ICANS

Armour et al. provided a comprehensive anatomic study of the ICANS in the human heart by delineating the locations of the major ganglionated plexi and their axonal fields and peripheral ganglia. This study demonstrated that the ICANS is “distributed more extensively than previously considered.”

Figure 3: CARTO map showing the localization of the GP adjacent to the 4 PVs by high frequency stimulation (HFS) from an electrode catheter placed endocardially subjacent to each of the epicardial fat pads containing the GP. Note that the encircled red dots indicate the sites at which a marked slowing of the ventricular rate was observed during HFS applied at that site (see Figure 4).
Further elaboration of the anatomy of ICANS has been published by Pauza et al. In essence these studies revealed that there is an extensive neural network covering, not only the atria but also both ventricles [Figure 1]. The major modulating centers reside in the clusters of neuronal bodies collectively housed in ganglionated plexi (GP), which, in turn, are located within fat pads. Of interest, 4 of these GP lie adjacent to the four PVs and have been reported to contain 200 or more neuronal cell bodies. On the other hand, as many as 1500 ganglia have been estimated to be found on the atrial and ventricular epicardium.

Figure 2A illustrates the “right” fat pads associated with the right pulmonary veins (RSPV, RIPV) in a patient undergoing thorascopically guided surgery. The anterior right (AR) GP is found within the large fat pad lying between the right PVs, whereas the inferior right (IR) GP is located within the smaller fat pad close to the inferior junction of the right and left atria. It should be noted that the ARGP and IRGP are to the left of Waterston’s groove (also known as the sulcus terminalis) which marks the boundary between the left and right atria. Although the right PVs are seen through a right thoracotomy their entrance into the left atrial chamber confirms the location of these PV and their associated GP as left atrial structures.

A thorascopic view of the left side [Figure 2B], locates the superior left (SL) GP and inferior left (IL) GP in fat pads at the LSPV/pulmonary artery junction and inferior posterior LIPV border, respectively. These GP can be located during endocardial catheterization procedures for AF ablation by electrical activation with high frequency stimulation (20 Hz). This results in marked slowing of the ventricular response during AF, at least a ≥ 50% increase in R-R interval.

**Figure 4:** A typical response to HFS at a GP site during ongoing AF which consists of a marked slowing of the ventricular response due to an initial strong parasympathetic effect causing suppression of A-V conduction for about 3 seconds. With termination of GP stimulation the ventricular rate is quickly restored.
increase in the R-R interval [Figure 3]. In this way the major locations of the GP can be delineated on a CARTO map [Figure 4]. It should be mentioned that other GP can be found on the heart itself, e.g., within the ligament of Marshall as well as on the large vessels within the pericardium, e.g., the right pulmonary artery and at the base of the aorta/pulmonary artery intersection.

Role of ICANS in Relation to AF-Basic studies

An early report by Sharifov et al implicated autonomic neurohumors, which were injected into the sino-atrial artery, in the initiation of AF. Subsequent basic studies addressed some of the fundamental questions arising from the clinical breakthrough findings that patients with paroxysmal AF have focal firing that arose from the myocardial sleeves which invest the PVs. As mentioned previously, another key finding was reported by Nademanee et al describing the distribution of CFAE in the atria in patients with AF. The abnormal PV firing was thought to provide the triggers for AF, whereas the CFAE was apparently an important constituent of the substrate for this form of AF since ablation at these sites was associated with a high rate of termination of AF. From these observations three critical questions arise.

Question 1. How does the focal firing in the PVs become converted into AF and not just manifest as atrial tachycardia? Scherlag et al demonstrated that the number of stimulated impulses applied to the PV would not induce AF unless there was simultaneous activation of the GP adjacent to that PV. Of importance, GP activation is achieved with electrical stimulation using high frequency (20 Hz) and very short stimuli duration (0.1 ms). During sinus rhythm, these stimulation parameters, which slow the heart rate, are delivered at a voltage that does not excite the atrium but does activate the neuronal clusters found in the fat pads on

Figure 5: The effect of locally applied acetylcholine (ACH) on the conversion of a Type I electrogram to one showing various forms of fractionation, i.e., complex fractionated atrial electrogram, (CFAE). Traces include ECG lead II, His bundle recording (HB), bipolar electrograms from the right (R) and left (L) atrial (A) free walls, R and L pulmonary veins (PVs) and right atrial appendage (RAA). Panel A. The trace labeled RAp represents a bipole on an electrode catheter which showed a Type I electrogram during AF (no CFAE). It was chosen to be locally painted with various concentrations of Ach. Panel B. There was no change when Ach, 1mM was applied to this bipole (no CFAE). Panel C. However, when 10mM Ach was applied to this site intermittent CFAE was noted. Panel D. The subsequent local application of 100mM Ach resulted in the appearance of continuous CFAE. See text for further discussion. (Reproduced with permission from Lin et al J Cardiovasc Electrophysiol 2007;18:1197-1205).
Question 2. What is the mechanism whereby the PVs rather than other atrial regions become the sites of focal firing in those patients with AF resistant to drugs and cardioversion? Po et al. caused focal firing in either the right or left superior PV after injecting the neurotransmitter acetylcholine (Ach) into the GP anatomically adjacent to those PV. Furthermore, additional studies by Patterson et al. provided additional evidence suggesting that PV myocytes show distinctive cellular electrophysiological differences from adjacent atrium, particularly, a shorter action potential duration (APD). Moreover, the PV tissue exhibited greater sensitivity to both cholinergic and adrenergic stimulation than adjacent atrial tissue. Thus, local stimulation of nerve endings in the PV induced release of acetylcholine which further shortened APD while release of the adrenergic neurotransmitters induced early after depolarizations (EADs) leading to rapid, triggered firing. The underlying mechanism for the EADs relates to the temporal disproportionality between the very short APD and the longer lasting calcium transient in the PV myocytes. Under autonomic stimulation these differences are further exacerbated so that the effects on the sodium-calcium exchanger favors excess calcium entry thereby leading to EAD formation, i.e., triggered PV firing. Lemola et al. performed PV isolation in dogs while preserving the GP and then ablated the GP while leaving the PV intact. Using vagal induced AF in both cases they concluded, “it is the PV associated ganglia not the PV themselves that are important in vagally mediated AF promotion.”

Question 3. In regard to substrate alterations, it has been suggested that PV isolation affects the substrate for AF maintenance. Yet, what exactly constitutes the AF substrate has not been clearly defined. The most specific substrate feature that has been identified has been the prevalence of CFAE whose ablation resulted in at least a 20% increase in AF ablation success compared to PVI alone. As such this approach has been incorporated into the stepwise ablation procedures used in many centers (see below). However, the mechanistic basis for this electrogram characteristic had not been elaborated. To test the hypothesis that autonomic factors might be responsible for CFAE, Lin et al. applied different concentrations of Ach to local atrial sites during sustained AF. These sites were chosen specifically because the bipolar electrograms manifested stable Type I potentials, i.e., regular, rapid activation separated by diastolic isoelectric intervals. Local application of 1 mM Ach to this electrogram site showed little, if any change in the electrogram morphology. On the other hand, local application of 10 mM and 100 mM resulted in a change from Type I to intermittent CFAE and continuous CFAE, respec-
tively

Role of ICANS in Relation to AF-Clinical studies

Ablation Strategies not Involving PVI

A report from Platt et al. described the identification of the GP at the PV-atrial junctions by applying high frequency stimuli to these nerve clusters, endocardially. In patients with persistent forms of AF, the response was a marked slowing of the ventricular response (≥ 50%) during AF. Ablation of these GP terminated the persistent AF in the 23/26 patients who had a complete study with an overall success rate of 96% during a 6 month follow-up. Lemery et al. concluded, “Ganglionated plexuses can be precisely mapped using high-frequency stimulation and are located predominantly in the path of (PVI) lesions delivered during ablation of AF.” More recent studies have reported wide ranging results after ablation of GP alone. Scanavacca et al. studied 7 patients with vagotonic AF in whom GP were identified by electrical stimulation (epicardially or endocardially) followed by GP ablation. Five of the seven patients showed AF recurrences over a follow up period ranging from 5-15 months. These authors concluded that ablation of GP may prevent AF recurrences in “selected” patients with apparent vagal induced paroxysmal AF. Katritsis et al. compared the results of GP ablation alone in 19 patients with paroxysmal AF and 19 age and gender matched patients who had circumferential pulmonary vein ablations. It should be pointed out that, in this study, GP ablation was performed based on anatomic identification of GP sites. No high frequency electrical stimulation was used to identify the GP or determine that they were ablated after radiofrequency applications. Nevertheless, arrhythmia recurrence was found in 14 of 19 (74%) with GP ablation vs, 7 of 19 (37%) with circumferential ablation during a 1 year follow-up. In contrast, Pokushalov et al. also used an anatomic approach to identify the location of the GP and then applied radiofrequency energy to ablate these sites. After a 1 year follow-up in 58 patients with persistent and long standing persistent AF (75%) and paroxysmal AF (25%) they reported an overall success rate of 86% during a short follow-up of 7 months. Danik et al. reported on a series of 18 patients whose AF duration averaged 5 years despite various drug regimens. These investigators were able to induce AF with burst pacing after acute GP ablation in 17 of 18 patients but after a 1 year follow-up freedom from AF recurrence was 94% in this same group.

Given the diverse outcomes reported by several investigators, it is important to establish some criteria for GP localization so that the optimal number of GP are effectively ablated in order to obtain results equivalent to PVI or better if PVI and GP ablation are combined (see below). A clinical example of partial GP ablations can be seen from Scanavacca et al. [figure 3]. Both epicardial and endocardial sites showing a “vagal” response before but not after ablation were relegated to the posterior wall of the left atrium. It would appear that the anterior aspect of the left atrium, where the largest of the GP is located [figure 1], was not ablated although a parasympathetic response was elicited at this site. The high AF recurrence rate of patients in this study may have been due to partial ablation of the major GP located at the PV atrial junctions.

Combination of GP Ablation and PVI Procedures

The first clinical study showing the relatively long term success of a combination of GP ablation and PVI was reported by Pappone et al. In a nonrandomized study of 297 patients with paroxysmal AF, undergoing left atrial circumferential ablation to isolate the pulmonary veins, these investigators found that some 34% showed marked slowing of the ventricular response along with hypotension during the application of radiofrequency energy to 4 specific areas adjacent to the PVs. Continued energy application consistently terminated this “vagal reflex.” In a 12 month follow-up, those 102 patients showed a 99% freedom from AF, whereas the others had a success rate of 85% over the same follow-up period. These workers were obviously impressed by these results, so much so, that their closing suggestion was: “Vagal reflexes can be elicited in several specific sites around all PV ostia and should be specifically targeted to cure paroxysmal AF.” Subsequent studies from this group have not indicated that this advice has been followed. However, there have been other studies using either endocardial catheter ablation or
surgical approaches which have performed both PVI and GP ablation. For example, in the small series reported by Scanavacca et al. 55 in which GP ablation alone accounted for a success rate of 25%, the addition of PV isolation showed a 100% success during a follow up of 250 days. In the study by Danik et al. [58], even though, with GP ablation, in 18/19 patients AF was acutely inducible, the same group with both GP ablation and PVI after a 1 year follow-up had only one recurrence of AF; a success rate of 94%. In a larger series of 83 patients with paroxysmal and persistent AF, Nakagawa et al. 60 reported that the freedom from symptomatic AF and AT at 22 months was 86% after a single procedure targeting both GP and performing an antral type PVI.

Surgical Reports Combining PVI and GP ablations

Using minimally invasive surgical techniques, the results of combined PVI and GP ablation have been more consistent and more encouraging. McClelland et al. 61 over a 1 year follow-up, had 14/16 patients showing and overall success rate of 87.5%. Mehall et al. 56 using the same techniques found 14/15 patients free of AF after a short 6 month follow-up. Matsutani et al. 63 reported the results of a combined Japan-United States experience using a “thorascopic mini-Maze” procedure for bilateral PVI plus ablation of the epicardial GP. They found 18 patients (90%) were free of AF over a mean follow-up of 17 months. Some surgical groups have been applying the combined PVI plus GP ablation approach in order to prevent post operative AF. Onorati et al. 64 compared two groups of patients with AF undergoing mitral valve surgery. Group A (44 patients) underwent left and right mini-Maze procedure, i.e., PVI using a bipolar clamp radiofrequency device; whereas, Group B (31 patients) had the PVI plus fat pad resection along the Waterston’s Groove, left pulmonary veins and Marshall’s ligament. GP were intra-operatively mapped and fat pad specimens sectioned and analyzed for presence of GP. At 13 months of follow-up, free freedom from atrial fibrillation or atrial tachycardia without anti-arrhythmic drugs was 73% in Group A and 93% in Group B. Doll et al. 65 studied 12 patients who had valve or coronary artery bypass graft procedures but also had AF. The average duration of AF was 4.5 years, although 5 patients had the paroxysmal form. After a 1 year follow up, 83% were in sinus rhythm and there were no recurrences of AF in the 5 with the paroxysmal form.

The GP Hyperactivity Hypothesis: Evidence that GP Stimulation Promotes AF Initiation and Maintenance

Based on the presently accumulated data, the approach, either endocardial or surgical, combining PVI and GP ablation shows a markedly increased success rate compared to PVI or GP ablation alone. As previous investigators 19, 20 have surmised, self sustaining AF would require both an inducing trigger and an appropriate substrate for maintenance. For the macro-reentrant or multiple wavelet form of AF, atrial premature beats (triggers), a markedly shortened and dispersed refractory period found in the remodeled atria, would provide the substrate for AF maintenance 66. Of interest this form of AF has been shown to be readily terminated by multiple class drug therapy. 67 On the other hand, in the drug resistant form of AF, we postulate that the trigger for focal firing at PV 17,18 or non-PV sites 22,23 is caused by hyperactivity of the major GP adjacent to PV ostia 48 or those associated with the myocardial sleeve into the superior vena cava 68 or within the ligament of Marshall. 23 Intermittent bursts of neural activity in these hyperactive GP release high concentrations of cholinergic and adrenergic neurotransmitters at susceptible sites, shortening refractory periods and inducing EADs as described above 48-50 thereby, providing the basis for triggered firing and subsequent AF. The same GP hyperactivity can extend through the interconnected neural network 69 causing excessive release of neurotransmitters at multiple nerve endings leading to CFAE 52, the latter serving, in large part, as the substrate for maintenance of AF.

Possible Mechanism Underlying GP Pathology

Invoking the GP hyperactivity hypothesis engenders the question regarding the pathologic basis underlying the development of this dysautonomia. Preliminary evidence from basic studies 20,21 indicate that the extrinsic autonomic input to the heart, i.e., from the brain and spinal cord, exerts an inhibitory control over the ICANS suggesting
that attenuation or loss of this control would allow the GP to become independently hyperactive. Presumptive evidence in support of this hypothesis can be inferred from the recent reports describing the incidence of AF in patients with heart transplants. Khan et al. 72 did a retrospective analysis of 923 patients who underwent orthotopic heart transplantation. This group was age, gender and body mass index matched versus a coronary artery bypass graft group. The differences in the onset of AF over a 3-7 year period were 0.3% for the former and 21% for the latter cohort. All the transplants, except 3, were done using the biatrial technique, whereby the major portion of the recipients atria are left and a remnant of the two atria from the donor are sutured to the recipient’s atria. Thus the major GP and their extrinsic innervation remain intact allowing control by the higher centers over the ICANS. The authors’ state, “….we did observe that the only cases of AF were all in patients who had bicaval anastomosis.” These three patients lost connection and supposedly control between the extrinsic autonomic innervation (from recipient) and GP of the donor heart. Since the PV in both types of anastomoses are isolated the possible source of the triggering for AF might well arise from the superior vena caval myocardial sleeve due to hyperactivity of the adjacent GP. 68

Progression of AF: From Paroxysmal to Long Standing Persistent Forms

The stochastic nature of GP firing 37 is consistent with the episodic nature of paroxysmal AF. Insofar as AF progression from paroxysmal to persistent and long standing persistent forms, the same remodeling mechanisms described for the progression of the multiple wavelet form of AF would come into play as the paroxysmal AF burden increased. In addition, more and prolonged episodes of AF have also been shown to result in autonomic remodeling which manifests as a greater propensity for AF inducibility. 73 It is likely, that both electrophysiological and autonomic remodeling factors are involved in the “AF begets AF” phenomenon, thereby allowing the coexistence of the neurally based drug resistant focal AF and the myocardial based macro- or multiple reentrant forms of AF. 74 Indeed, this coexistence, previously predicted 19,20 could explain the findings of Danik et al. 58 who induced AF after acute GP ablation in 17 of 18 patients but showed long term (1 year follow-up) freedom from AF recurrence in 94%. Also, others have reported that drugs that were ineffective prior to GP ablation could be used to maintain sinus rhythm in patients still inducible after GP ablation and PVI. 75

The PVI Paradox

Finally, another reported, apparently paradoxical, effect of PVI may be explained by the hyperactive GP hypothesis. Numerous investigators 35-36 have concluded, “Complete electrical isolation of the PVs is not a requirement for a successful outcome after LACA”. 25 It should be noted, that although the major GP, containing hundreds of neurons, are situated close to the PVs, there are many other GP with few neurons throughout the atria. 41 The interruption of axons from these hyperactive GP to PVs may have also contributed to PV focal firing. A recent experimental study showed that myocardial conduction block could be achieved across the atrial appendages but that subsequent application of Ach to the appendage could cause focal firing arising from the PV via unblocked neural connections. 76 The converse can also be predicted, if one accepts the existence of both a neural as well as a myocardial conduction system throughout the heart [41, Figure 1]. It seems possible that in some cases, neural connections can be interrupted from atria to PV while myocardial conduction may return.

By recognizing these diverse pathologies developing within this dual cardiac conduction system, i.e., neural as well as myocardial, new insights into the diagnosis of various cardiac arrhythmias, besides AF, may emerge and provide potential new therapeutic approaches to their prevention or termination.

Conclusions

In this review we have summarized the favorable aspects and drawbacks of pulmonary vein isolation (PVI). As for the role of the ganglionated plexi (GP), found adjacent to the PV atrial entrances, both basic and clinical evidence has shown that GP stimulation promotes initiation and maintenance of AF, and that GP ablation reduces recurrence of AF following catheter or surgical ablation of these structures. Based on
these findings, the GP Hyperactivity Hypothesis has been proposed to explain, at least in part, the mechanistic basis for the focal form of AF. In addition, the co-existence of both a myocardial and neural conduction system in the atrium can aid in understanding the greater success for AF ablation by the combined use of PVI and GP ablations.

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References


Atrial Fibrillation Ablation: First-Line Therapy?

Atul Verma MD
Southlake Heart Rhythm Program, Division of Cardiology, Southlake Regional Health Centre, Newmarket, Ontario, Canada.

Abstract

Background: Ablation for atrial fibrillation (AF) is a widely-accepted treatment for this arrhythmia. Ablation is traditionally reserved for second-line therapy in patients who have failed drug therapy, but it may be ready for first-line treatment.

Objective: This article outlines the rationale for using ablation as first-line therapy for AF.

Findings: AF increases both morbidity and mortality. Unfortunately, drug-based therapy for AF is very ineffective and may contribute adversely to both patient morbidity and mortality. Ablation addresses the root causes of AF and thus may be curative. The technique for ablation has become quite consistent and the outcomes better than those with drug therapy. The complication risk is also acceptably low. There is even preliminary evidence to suggest that AF ablation is superior as first-line treatment compared to drugs.

Conclusion: AF ablation is rapidly evolving towards becoming first-line therapy for some patients with this debilitating arrhythmia.

Key words: Atrial fibrillation, Pulmonary veins, Catheter ablation, Review.

Introduction

Atrial fibrillation (AF) is an increasingly common disease, affecting both patient morbidity and mortality. Drug and device-based treatments for AF are palliative, but not curative. AF ablation has emerged as a promising new treatment strategy offering the possibility of a cure. However, by guidelines, ablation is only considered “second-line” therapy for highly symptomatic patients who fail antiarrhythmic medications. As AF ablation achieves more consistency with higher success rates and fewer complications, the procedure may be getting closer to “prime-time” and may eventually be considered as first-line therapy for selected patients in experienced centers. ¹

Importance of Maintaining Sinus Rhythm

Clinical trials such as AFFIRM (AF Follow-up Investigation of Rhythm Management), ² RACE (Rate Control versus Electrical Cardioversion for AF), ³ and STAF (Strategies for Treatment of AF) ⁴ have compared a strategy of rate control versus rhythm control using antiarrhythmic drugs. All of these trials reached the same conclusion: there is no mortality difference between the two approaches and that rate control may suffice for most patients with AF. Although these conclusions suggest that sinus rhythm may confer no benefit to AF patients, this is not the case. These trials were not comparisons of sinus rhythm versus AF, but a comparison of a rate control strategy...
to a rhythm control strategy that tried to maintain sinus rhythm. However, the success rates of the rhythm control arms were only 20-40%. Additionally, 10-35% of patients in the rate control arms were spontaneously in sinus rhythm. Thus, it is not fair to look at these studies as true evaluations of the benefit of sinus rhythm.

When the data from these trials is analyzed according to the patient’s actual rhythm (as opposed to their treatment strategy), the benefit of sinus rhythm over AF becomes clear. An “ontreatment” analysis from the AFFIRM investigators demonstrates that the presence of sinus rhythm was one of the most powerful, independent predictors of survival even after adjustment for all other risk factors. The survival benefit was offset in the trial by the increased mortality conferred by antiarrhythmic drugs. Reduced mortality attributable to sinus rhythm has been shown in other studies. These findings are also consistent with large population-based studies that have long shown the negative independent prognostic impact of AF on survival.

Finally, AFFIRM and the other trials largely excluded patients who were very symptomatic with their AF. This is an important group that clearly benefits from sinus rhythm and represents more than one-third of all AF patients.

**Drug and Device-Based Rhythm Control Works Poorly**

Unfortunately, drug and device-based treatments for AF are poor in maintaining sinus rhythm. In the device realm, burst atrial pacing often fails to terminate or minimize AF. Atrial defibrillators acutely terminate AF, but the need for repeated shocks is hard for patients to tolerate. Multisite atrial pacing has also failed to demostrate any consistent reduction in AF burden. Antiarrhythmic medications (AAM) are the most widely used treatments for rhythm control but their efficacy is borderline. Amiodarone is the most effective AAM, with a 65% 1-year efficacy rate in comparison to sotalol or propafenone in the CTAF study. However, the actual success of amiodarone is likely lower than this reported result. First, CTAF did not include a placebo arm, so we do not know how many patients would have maintained sinus rhythm spontaneously. In a recent meta-analysis of randomized trials on AAM, the incremental treatment effects over placebo were only 21.5%, 33.1%, and 17.4% for class IA, IC and III agents respectively. An AFFIRM trial substudy showed that the success rate of amiodarone was only 60%, compared with 23-38% for other AAMs and 35% for placebo. Thus, AAM are at best a palliative measure to reduce AF. Although reduction of AF burden may be considered a treatment success for some patients, it may not be enough. Small AF burdens can still increase morbidity and mortality and the cutoff for defining a “low-risk” AF burden has not been defined. Furthermore, even brief recurrences may be too much in severely symptomatic patients.

AAM are also associated with debilitating side effects. Discontinuation rates for AAM range from 11-40% in most trials. Amiodarone is the most effective AAM, but also has the most dangerous side effect profile. Within five years, more than 30% of patients on amiodarone will discontinue treatment because of intolerance. Skin discoloration, pulmonary fibrosis, symptomatic thyroid problems, and neurological/ophthalmic side effects will occur in 2-4% of patients each. Even worse, AAM treatment can increase patient mortality. This paradigm has been long known, given the results of the CAST and SWORD trials where class I agents and d-sotalol increased mortality when given post-myocardial infarction. Both cardiac mortality and arrhythmic death significantly increased in patients on AAM in the Stroke Prevention in AF study. Analysis of the AFFIRM trial reveals a similar disturbing trend. When adjusted for other variables, use of AAM was associated with an increased risk of mortality in spite of the presence of sinus rhythm (hazard ratio 1.49, p=0.0005). Interestingly, noncardiac death increased in the AAM group, which revealed higher rates of both pulmonary and cancer-related mortality. While the direct relationship is not clear, the AFFIRM investigators point out that amiodarone, in particular, has been previously associated with higher non-cardiac mortality in both the EMIAT and AVID trials.

Newer drug therapies are currently in development, but as of yet, none are clinically available. It is also unclear that any of these agents, including
dronaderone, will have an efficacy that is equal to, let alone better than, amiodarone. Finally, these agents may have their own limitations, especially in patients with congestive heart failure or other structural heart disease.

**AF Ablation Offers a Curative Option**

In contrast to AAM, catheter ablation offers the possibility of curative therapy. Most agree that the endpoint of current AF ablation is to electrically “disconnect” the pulmonary veins (PVs) from the rest of the atrium by ablating around the origin of the veins. That is because the PVs play a major role in both triggering and maintaining AF. Rapid discharges from the PVs initiate fibrillatory conduction with non-PV triggers occurring in no more than 10% of patients. AF is also sustained by pe-

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**Figure 1**: Panels depicting the similarity in location of the radiofrequency lesions produced by various groups’ approaches to atrial fibrillation ablation. The upper left panel shows an outer view of a patient’s left atrium as seen from the posterior aspect using three-dimensional, multislice computed tomography. Seen clearly are the tubular portions of each of the four pulmonary veins (individually labeled). The borders between the antra of the pulmonary veins and the posterior wall of the left atrium are indicated by the small white arrows. The upper right panel shows a three-dimensional electroanatomical map (CARTO, Biosense Webster Inc.) of the left atrium (same patient as panel above) acquired during atrial fibrillation ablation guided by intracardiac echocardiography (ICE). Using ICE, the borders of the pulmonary venous antra can be accurately defined and lesions can be placed to completely surround and electrically isolate the antra. The red dots represent the anatomical locations of these lesions produced by ICE-guided ablation. The lower panel shows the location of lesions produced using a CARTO-guided approach described by Morady and colleagues. In both cases, the location of the lesion sets is similar, encompassing the anterior and posterior borders of all four pulmonary venous antra. LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein. (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams & Wilkins).
riodic micro-reentrant circuits, or “rotors,” which are localized primarily in the left atrial (LA)-pulmonary vein junction. 25,26 Autonomic inputs may also be very important in triggering and maintaining AF, and appear to be clustered around the PV-LA junctions. 27

Having understood how AF ablation works, the technique has become much more consistent. Initially, there existed a multitude of methods for ablating AF. 24 Some targeted triggered activity in “culprit” PVs only, while others circumferentially ablated around one or more of the PVs. Others attempted to mimic the surgical Maze procedure by creating linear lesions. Today, most centers are empirically isolating all four PVs, since any one may become a triggering focus over time. 28 Furthermore, most groups now ablate outside of the tubular portion of the PV to avoid PV stenosis and improve efficacy. This makes sense given that the PV is funnel-shaped with a large proximal end, referred to as the “antrum,” which blends into the posterior wall of the LA. Therefore, to encompass as much of the PV structure as possible, ablation needs to be performed around the entire antrum, along the posterior left atrium. 29 Although ablation in this region is referred to by different names, such as “circumferential PV antrum ablation,” or “extraostial isolation,” the lesion sets produced by the procedures are all very similar (Figure 1).

With growing experience, AF ablation has proven itself to have consistent success rates as reported by several groups. In the past, success rates ranged widely from 6-93%, 24 but these studies were published very early on in the ablation experience. Furthermore, the definition of “success” varied with some groups using off-drug cure as the definition of success while others included patients in sinus rhythm on AAMs. Recent publications of extraostial PV isolation show a consistent cure rate off drug therapy of 80.5% overall (Table 1). 30,35 A further 10-20% become responsive to previously ineffective AAM. 36 The cure rates are not 100%, but they are two to three times better than AAMs. Furthermore, the results seem durable, given that very late recurrences beyond one year are rare. 37 These results are now being confirmed in multicenter, prospective clinical trials, as opposed to solely single-center experiences. Success rates of ablation may even get better as adjuvant lesions are applied in conjunction with PV antral isolation, such as linear lesions, 38 ablation of fractionated electrograms, 39 or targeting regions based on spectral analysis. 40 And while initial studies included only paroxysmal patients with

Table 1

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Year</th>
<th>Pts</th>
<th>Age (years)</th>
<th>Parox Tool(s)</th>
<th>Endpoint</th>
<th>AF-Free (off drugs)</th>
<th>Follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouyang et al. [44]</td>
<td>2005</td>
<td>100</td>
<td>60±9</td>
<td>88%</td>
<td>CARTO</td>
<td>PV Isolat’n</td>
<td>71%* 240</td>
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<tr>
<td>Hocini et al. [42]</td>
<td>2005</td>
<td>90</td>
<td>55±9</td>
<td>100%</td>
<td>NAVX</td>
<td>PV Isolat’n</td>
<td>87% 450</td>
</tr>
<tr>
<td>Mansour et al. [43]</td>
<td>2004</td>
<td>40</td>
<td>55±10</td>
<td>80%</td>
<td>CARTO</td>
<td>PV Isolat’n</td>
<td>75% 330</td>
</tr>
<tr>
<td>Kanj et al. [41]</td>
<td>2007</td>
<td>180</td>
<td>59±9</td>
<td>86%</td>
<td>ICE</td>
<td>PV Isolat’n</td>
<td>80% 270</td>
</tr>
<tr>
<td>Oral et al. [40]</td>
<td>2006</td>
<td>77</td>
<td>55±9</td>
<td>0%</td>
<td>CARTO</td>
<td>EGM Red’n</td>
<td>74% 365</td>
</tr>
<tr>
<td>Pappone et al. [39]</td>
<td>2006</td>
<td>99</td>
<td>55±10</td>
<td>100%</td>
<td>CARTO</td>
<td>EGM Red’n</td>
<td>86%† 365</td>
</tr>
<tr>
<td>Total</td>
<td>586</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79.3%</td>
</tr>
</tbody>
</table>

PAbbreviations: AF=atrial fibrillation, CARTO=electroanatomical mapping system (Biosense Webster), EGM Red’n= reduction of local EGM amplitude (usually >70%), ICE=intracardiac echocardiography, PV Isolat’n = pulmonary vein isolation, NA=not available, NAVX = electroanatomical mapping system (St Jude Medical)

* Success was 95% off drugs after a second procedure
† Success was 93% off drugs after a second procedure
minimal structural heart disease, good results can now be obtained in persistent AF, \(^4^1\) patients with heart failure,\(^4^2\) hypertrophic cardiomyopathy, \(^4^3\) moderate valvular heart disease, \(^4^4\) and advanced age. \(^4^5\) The incidence of complications with AF ablation is also very low, and continues to fall as experience grows. Complications include vascular complications cardiac perforation/tamponade, valvular injury, embolic stroke or systemic embolism, esophageal injury, PV stenosis, and proarrhythmia due to reentrant tachycardias. When only recent reports using a more consistent technique are reviewed, the complication rates low (Table 2). The complication rates are continuing to fall with more recent modifications to the technique. Higher ACT levels of 300-400 sec can reduce thromboembolic risk. \(^4^6\) Esophageal injury can be avoided with strict limitations on RF energy output. \(^4^7\) Procedural-related atrial flutters can also be reduced to < 5% if care is taken to document total electrical isolation of the PVs at the level of the antra and with the addition of linear ablation lesions, such as a line across the mitral valve isthmus. \(^4^8\) Newer technologies to reduce complications and improve the ease of performing ablation are also imminent, including robotic/magnetic-controlled catheter systems and balloon-guided systems.\(^5^0-5^2\) With such a high success rate and a low attendant complication rate, current evidence suggests that AF ablation may not only be better than medical therapy, but may reduce both the morbidity and mortality associated with AAMs. For example, strokes are uncommon among most post-AF ablation patients, so coumadin may be stopped in all but the highest risk patients. \(^5^3\) In a controlled, long-term study (median follow-up 900 days), 589 patients who underwent AF ablation had significantly improved survival compared to 582 matched patients who received AAM, \(^5^4\) although this study was a retrospective, singlecenter, population-matched study and not prospective. In a randomized pilot study comparing first-line ablation to first-line drug therapy, AF recurrence rates were significantly lower in the ablation arm (13% vs 63%, p<0.05) (Figure 2). Others have also reported similar results in head-to-head comparison \([30,5^5]\) and other trials are underway. Ablation is even more cost effective than medical therapy with the cost of ablation being offset by the higher cure rate within 2-4 years. \(^5^6\) 

First-Line Ablation May be Reasonable for Some

Based on all of the preceding arguments, AF ablation may be reasonable as first-line treatment for some AF patients. Large-scale, comparative clinical trials are still ongoing and this data will be required before recommending ablation as first-line for a very broad AF population. Patients with highly symptomatic paroxysmal or persistent AF and minimal structural heart disease experience considerable morbidity and mortality from AF. For these patients, AAM is not always effective and may be poorly tolerated. Therefore, if first-

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number</th>
<th>%</th>
<th>Range in Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Ischemic Attack</td>
<td>4</td>
<td>0.7%</td>
<td>0-5%</td>
</tr>
<tr>
<td>Permanent Stroke</td>
<td>1</td>
<td>0.2%</td>
<td>0-1%</td>
</tr>
<tr>
<td>Severe PV Stenosis (&gt;70%, symptomatic)</td>
<td>1</td>
<td>0.2%</td>
<td>0-1%</td>
</tr>
<tr>
<td>Moderate PV Stenosis (40-70%, asymptomatic)</td>
<td>0</td>
<td>0.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Tamponade/Perforation</td>
<td>6</td>
<td>1.0%</td>
<td>0-5%</td>
</tr>
<tr>
<td>Severe Vascular Access Complication</td>
<td>2</td>
<td>0.3%</td>
<td>0-5%</td>
</tr>
<tr>
<td>Phrenic Nerve Palsy</td>
<td>1</td>
<td>0.2%</td>
<td>0-1%</td>
</tr>
<tr>
<td>Atrioesophageal Fistula</td>
<td>0</td>
<td>0.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abbreviation: PV=pulmonary vein
line ablation is offered, it should at least be considered for those patients with symptomatic AF, mild-moderate structural heart disease, and paroxysmal or persistent AF. Ablation may particularly benefit younger patients with “lone AF,” for whom very long-term antiarrhythmic and potential anticoagulation may pose potential risk and cost.

There are obviously some patients in whom AF ablation may not every be a good option. Patients with extensive comorbidity or totally asymptomatic patients may not derive benefit. Patients with extensive atrial scarring or severe left atrial enlargement (>55 mm) also do not respond to ablation. Operator experience is also an important consideration when contemplating ablation. It is prudent that only centers with considerable experience in performing AF ablation should consider offering ablation as first-line therapy. Only these centers can offer the favorable risk-benefit ratios required to justify first-line ablation. As technology improves, however, robotic or magnetic controlled catheter navigation may help reduce the influence of operator experience.

Conclusions

AF is associated with both morbidity and mortality, so it is in the patient’s best interest to pursue effective and safe treatment to maintain sinus rhythm. AAMs are ineffective, and increase mortality. In experienced hands, AF ablation is an effective and safe treatment that offers an excellent chance for a lasting cure. Thus, AF ablation should be considered as a first-line option for selected patients with this disease.

References

1. Verma A, Natale A. Should atrial fibrillation ablation be considered? As technology improves, however, robotic or magnetic controlled catheter navigation may help reduce the influence of operator experience.

Figure 2: Kaplan-Meier curves depicting freedom from atrial fibrillation (AF) in patients undergoing AF ablation by pulmonary vein antrum isolation (PVI) compared to being treated with an antiarrhythmic drug (AAD) from the pilot study of the Radiofrequency Ablation for Atrial Fibrillation Trial (RAAFT). Seventy patients with symptomatic, mostly paroxysmal AF, were randomized to PVI (n=33) or AAD (n=37). Overall recurrence of symptomatic AF was 13% in the PVI group compared to 63% in the AAD group treated with their first drug (p<0.05, mean follow-up time 8.5±3.2 months). Even after patients were switched from a first AAD to a second AAD, recurrence still remained significantly higher compared to the PVI arm (p<0.05). (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams & Wilkins).
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Journal of Atrial Fibrillation

37. Heiweg MH, Tai CT, Tsai CF, et al. Clinical outcome of very late


Paroxysmal Lone Atrial Fibrillation Is Associated With An Abnormal Atrial Substrate: Characterizing The “Second Factor”

Charles R. Mitchell, MD and Mithilesh K. Das, MD

Krannert Institute of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

Introduction

Stiles et al, 1 recently published a study titled “Paroxysmal Lone Atrial fibrillation is associated with an abnormal atrial substrate: Characterizing the Second Factor” in The Journal of The American College of Cardiology.” Authors demonstrated structural and electrophysiological abnormalities in the atria of patients with paroxysmal lone atrial fibrillation (AF). The authors postulate that these factors are likely contributors to the “second factor” that predisposes to the development and progression of AF.

AF is the commonest arrhythmia encountered in clinical practice. It is associated with a poor clinical outcome and a high healthcare cost. It is classified as paroxysmal, persistent or permanent AF. Although each clinical class is distinct, a majority of patients with paroxysmal AF ultimately may suffer from the persistent or permanent AF due to lack of appropriate therapy and continued remodeling of the atria. Lone AF has been defined as AF in an individual less than 60 years of age with no classic cardiac risk factors. 2 Although lone AF is associated with a low incidence of morbidity, the natural history is that of a progressive increase in incidence and duration of episodes of AF, with many becoming permanent. 3 Present therapeutic approaches to AF have major limitations, including limited efficacy and significant adverse effect liability. Although, in the recent years, AF ablation has been shown to have a substantially improved success rate over antiarrhythmic drug, 4-7 it has not been completely successful, and has been associated with adverse events. The realization of AF progression in otherwise healthy subjects, coupled with the limitations of therapy mandate researchers to improve the understanding of the mechanisms underlying AF, with the premise that better mechanistic insights will lead to innovative and innovative therapeutic approaches. As such, there has been a wealth of research attempting to elucidate the causes of the onset of AF and its progression.

In the study by Stiles et al, 1 the authors electrophysiologically characterized the atrial substrate of 25 highly symptomatic patients with documented paroxysmal lone AF, who were undergoing first-time ablation for AF. They compared these patients with a reference group of 25 patients with no history of AF, who had atrioventricular re-entry tachycardia, and were undergoing ablation of a left-sided pathway. All of the patients had structurally normal hearts and no known risk factors for cardiac disease. In an attempt to isolate the chronic, underlying abnor-
mality from any acute electrophysiologic effects of AF, only patients with no AF documented on continuous monitoring for the week prior to the study were enrolled. During electrophysiologic study, four catheters were positioned in the atria of these patients, including a coronary sinus catheter, a 10-pole “crista” catheter, a 20-pole catheter along the lateral right atrium, and a 10-pole roving catheter positioned at sites in the left atrium via a sheath across the atrial septum. Effective refractory period (ERP), conduction velocity (CV), and site-specific conduction abnormalities along the crista terminals were measured. Electroanatomical mapping was conducted, with creation of voltage and activation maps of the atria. The proportion of fractionated electrograms, including fractionated signals and double potentials, were recorded as well. There are two major findings of this study as discussed below:

1. Structural Remodeling and Electrophysiological Properties of the Atria in Lone AF

The study demonstrated that when compared with reference group, lone AF is associated with significant structural abnormalities characterized by atrial dilation and loss of endocardial voltage. The patients with AF had significantly larger left atrial size at baseline than the reference group (41 ± 7 mm vs. 34 ± 4 mm P<0.001). The left and right atrial volumes were enlarged by 27% and 36%, respectively. There were lower mean atrial voltage (right atrial and left atrial voltages were lowered by 41% and 48%) in lone AF patients, suggesting the loss of atrial myocardium.

Lone AF is associated with significant P-wave prolongation by 35%, atrial refractoriness lengthening by 10%, intra-atrial conduction decrease between 21% and 45%, and a significantly higher proportion of fractionated and complex electrograms, when compared to the reference group. The mean ERP of the patients with AF was significantly increased over the reference patients (at 800 ms: 255 ± 25 ms vs. 222 ± 16 ms, p<0.001; at 600 ms: 234 ± 20 ms vs. 212 ± 14 ms, p=0.004) with no significant difference in the heterogeneity of refractoriness.

Electroanatomical mapping showed larger volumes, lower mean bipolar voltage, a slower mean conduction velocity, and a prolonged total atrial activation time in the AF group as compared to the reference group. Evaluation of complex electrograms showed significantly greater proportion of points with double potentials or fractionated signal in the AF group than the reference group (27 ± 8% vs. 8 ± 5%, p<0.001).

Since the early models of AF, it has been shown that the arrhythmia itself causes electrophysiological changes in the atrial substrate, including a shortening and heterogeneity of the atrial refractory period, and prolongation of the sinus node recovery time, which can lead to further AF. These studies yielded the conclusion that “AF begets AF,” however, aggressive attempts at cardioversion or antiarrhythmic drugs to maintain sinus rhythm may slow but has failed to prevent the progression of this disease. Therefore, authors suggested that “sinus rhythm does not beget sinus rhythm” in lone AF. Mechanistically AF is thought to be due to the interaction between a trigger and atrial substrate. In 1972, Zipes et al. demonstrated electrical activity within the thoracic veins. Twenty seven years later, Haissaguerre et al. identified a focal source of electrical discharges within the pulmonary veins as a source of AF and opened the door to a new potential treatment modality and new mechanisms of AF. However, treatment of triggers has not been successful in all patients with paroxysmal or lone AF. On the contrary, substrate modification along with the treatment of triggers of persistent and permanent AF has been effective, at least, in few patents. Several studies try to investigate the substrates and associated risk factors involved the pathogenesis of paroxysmal AF. A familial predisposition for AF has been frequently seen clinically. Mutations in potassium channels, sodium channels as well as connexins have been implicated in rare forms of monogenic AF, although no more common genetic link has been found. Multiple other risk factors such as obesity and weight gain, obstructive sleep apnea, inflammation, excessive endurance exercise, and toxins ranging from alcohol to caffeine have been shown to be associated with AF. Lone AF patients do not have any known risk factor for AF, yet sinus rhythm does not beget sinus rhythm in them. Of the electrophysiological findings of this study the one that stands out is a prolongation of the atrial ERP in patients with AF. Heretofore, evaluations of the ERP have been performed in the acute period, soon after conversion of AF, and have dem-
The tachy-brady syndrome is a common manifestation of SND and is the combination of abnormal automaticity (bradycardia) and abnormal conduction properties of the atrium which predispose patients to AF and other atrial arrhythmias. Conversely, proportion of patients with SND who receive a pacemaker suffer from AF during follow-up. This study, like others, has demonstrated that AF is associated with significant electrophysiological and structural remodeling. Furthermore, SND encountered in patients with paroxysmal or persistent AF, can reverse with catheter ablation of AF. It is possible that SND and AF are interrelated and may be the two spectrums of the same disease or at least share some common mechanisms, with clinical symptoms that depend upon severity of these two arrhythmias.

The main limitation of the study is that patients with persistent AF were not studied; however, many patients with persistent AF start with paroxysmal AF initially and possibly the same “second factors” continue to work in this stage of the disease. Furthermore, patients were monitored only for a week before the procedure to ensure that the evaluation was remote from an episode of AF; nevertheless, an effect of rate-related remodeling from previous episodes cannot be excluded.

The study by Stiles et al, has shown that lone AF is associated with structural and electrophysiological remodeling of atria and the SAN. Whether “second factors,” are the result of progressive fibrosis, inflammation, or any of a number of other mechanisms is still remains to be elucidated. The authors, by studying patients remote in time from the arrhythmia itself, have been able to show that the predominant underlying substrate in patients with lone AF is structural and electrophysiological remodeling, perhaps accounting for the progression of the disease. Future strategies to treat paroxysmal or lone AF should, therefore, also focus on atrial substrate. It may be valuable since pulmonary vein isolation is currently considered to be only moderately successful (success rate 70-85%) for the majority of patients with paroxysmal AF. It is often difficult to predict which patient will have a recurrence of the arrhythmia after catheter ablation. This study showing an abnormal substrate in lone AF raises the possibility of progressive disease continuing despite early procedural success. Further study is needed to define the role of substrate

2. Abnormal Sinus Node Function

The study evaluated the baseline sinus cycle length, sinoatrial conduction time (SACT), and corrected sinus node recovery time (CSNRT). Patients with AF have an impaired sinus node function (the corrected sinus node recovery time was prolonged by 43%). AF patients had a longer baseline sinus cycle length (975 ± 131 ms, vs. 762 ± 129 ms, p<0.001), longer SACT (154 ± 58 ms vs. 83 ± 31 ms, p<0.001), and longer CSNRT at 600 ms (265 ± 57 ms vs. 185 ± 60 ms, p = 0.002), but not at 450 ms (261 ± 96 ms vs. 241 ± 76 ms, 9=0.6). These findings confirm an abnormal sinus node function in lone AF, although it cannot be defined as a clinically significant sinus node dysfunction (SND). With the progression of the disease to persistent AF, sinus node function can worsen. SND is an abnormality involving the generation of the action potential by the SAN and is characterized by an atrial rate inappropriate for physiological requirements. SND occurs in 1 in every 600 patients with heart disease above 65 years of age and accounts for approximately half of implantations of pacemakers in the United States. Several intrinsic or extrinsic factors may influence sinus node function, although age-dependent primary degenerative fibrosis of the tissues of the sinus node is thought to be the primary cause of SND. Manifestations of SND include symptomatic sinus bradycardia, sinus pauses, sinus node exit block, sinus arrest and chronotropic incompetence. A subset of patients with AF suffer from sinus node dysfunction (SND), which is defined as tachy-brady syndrome.
in recurrence of paroxysmal AF despite achieving a good pulmonary vein isolation and substrate modification. A combination of detailed noninvasive evaluation of atrial dimensions and function with echocardiography and/or enhanced magnetic resonance imaging techniques along with a high density mapping of the electrophysiological substrate (fractionated electrograms, dominant frequencies, CV, ERP, etc) as well as triggers (pulmonary vein and non-pulmonary vein sources) may be needed to improve the long-term success rate of AF ablation. The study provides an encouragement to find a “cure” for AF by identifying “second factors” and its role in disease progression.

References


Introduction

In July 2009, the federal Food and Drug Administration (FDA) approved the marketing of dronedarone (Multaq, sanofi-aventis) for use in patients with atrial fibrillation (AF) or flutter (AFL) [with a requirement for a recent episode] that is paroxysmal or persistent – the latter having been converted to sinus rhythm or with conversion planned – who have, in addition to AF, certain “high-risk” markers for adverse outcomes that were derived from the enrollment criteria for the landmark ATHENA trial. These markers include one or more of: age >70 yrs, hypertension, diabetes mellitus, prior cerebrovascular accident, left atrial size of 50 mm or larger, or LVEF <40%. Contraindications include class IV heart failure or symptomatic heart failure with a recent decompensation; second or third degree AV block without a functioning pacemaker; bradycardia < 50 bpm; concomitant use of a strong CYP3A inhibitor or a QT prolonging agent that may induce torsades de pointes; QTc Bazett interval of 500 ms or longer; or severe hepatic impairment.

This approval was the culmination of a developmental course that was detailed by Peter J. Zimetbaum, M.D. in his April 30, 2009 article in the New England Journal of Medicine entitled: Dronedarone For Atrial Fibrillation – An Odyssey. In this development process, dronedarone, an agent derived from amiodarone, with a similar but non-identical electrophysiologic profile, but with more user-friendly pharmacokinetics and an apparently much lower risk of toxicity – as was summarized in Dr. Zimetbaum’s manuscript-- was first proven superior to placebo in the suppression of atrial fibrillation in a mixed population of patients in the EURIDIS and ADONIS trials. In these trials dronedarone reduced the rate of recurrent AF from 75% to 64%; in addition, the ventricular rate during recurrences was reduced 12-15 bpm. The dose used was 400 mg bid – the only dose used in the pivotal trials for this agent, which is an outcome of its dose-ranging DAFNE trial in which higher doses were poorly tolerated due mainly to diarrhea as well as appearing less effective. The prohibition against its use in class IV heart failure or heart failure with recent decompensation was the result of the premature termination of the ANDROMEDA trial – a mortality and morbidity trial in patients with LVEF 35% or lower and decompensated symptomatic heart failure – in which the trial was terminated early due to excess mortality and hospitalization risk on the active agent as compared to placebo. The requirement for additional cardiovascular risk markers in addition to AF/AFL and the specific indication for dronedarone – “to reduce the risk of cardiovascular hospitalization” in patients with AF or AFL with a recent episode “and associated cardiovascular risk factors” was derived from the dramatic findings in the ATHENA trial. ATHENA demonstrated, in 4628 patients with
a recent episode of AF or AFL and specific associated risk markers including those identified above, that dronedarone, as compared to placebo, was associated with a lower risk of the composite endpoint of death from any cause and hospitalization due to cardiovascular events. There was a non-significant trend towards reduction of total mortality. The reduction in cardiovascular hospitalization was largely due to a reduction in AF/AFL events requiring hospitalization – but, of note, time to first AF recurrence, the number of AF recurrences, and similar measures of AF burden were not outcome events measured in this trial. The results were generally similar in all subgroups that were assessed, including a variety of commonly used cardiovascular drugs. Also reduced were acute coronary syndrome, and, as shown in a post-hoc analysis, presented at the 2008 European Society of Cardiology meetings by Dr. Hohnlosser, stroke (independent of the use of anticoagulants).

Consequent to the approval of dronedarone, for the indication detailed above – which is not simply for the reduction of AF/AFL (i.e., for prolongation of the time to recurrence, the most common indication for drugs approved for the therapy of AF/AFL) – how are physicians likely to use this drug and what unknowns remain that may be necessary to learn in order to ultimately use dronedarone to its fullest and most appropriate potential. Perhaps the two major limitations at this point are the limited duration of long-term experience with the drug and limited comparative efficacy and tolerance/safety data. In the trials outlined in dronedarone’s “odyssey” the duration of follow up was generally 1 year with the longest follow up for any patient approximating 3 years. Thus, while in these trials dronedarone appeared to be free of the pulmonary, thyroid, and other toxicities that plague the use of amiodarone, we have to recognize that longer exposure without events will truly be re-

**Figure 1:** A suggestion for the application of dronedarone to the ACC/AHA/ESC algorithm.

**Panel 1:** patients with no or minimal heart disease
Panel 2: Patients with hypertension without significant hypertrophy

Panel 3: Patients with hypertension with significant hypertrophy: here, there is no significant published data to indicate safety for the specific use of dronedarone
Panel 4: patients with coronary artery disease

Panel 5: patients with heart failure
quired to assure us fully as to its chronic safety profile. Recall that some of amiodarone’s toxic profile is total dose and timeexposure dependent. Secondly, we have very limited comparative efficacy for dronedarone against other antiarrhythmic agents (AADs). The only such data that exits is that from the DIONYSOS trial in which dronedarone and amiodarone were compared in a 500 patient trial of only 6 months duration in which dronedarone demonstrated lower efficacy against AF than did amiodarone, but fewer adverse effects and a lower rate of drug withdrawal. Hence, how it might perform against other AADs either in the suppression of AF/AFL or in a trial similar to ATHENA is unknown.

So, where does all this information leave the clinician who now must incorporate it into his or her armamentarium? One view might be that given the dramatic outcome events demonstrated in ATHENA, dronedarone should be the first AAD tried in AF/AFL patients with a recent arrhythmic event and the associated cardiovascular risk profile that is part of the indication for this agent – it may be seen as unethical to do otherwise. Others may have less unbridled enthusiasm preferring to await longer-term safety data than currently exists and more comparative data than currently exists before taking such a strong stance. Personally, I find myself somewhere in between, but leaning towards the former and would propose that dronedarone has a role in each of the arms of the treatment algorithm outlined in the 2006 ACC/AHA/ESC guidelines as shown in the following figure that I have developed specifically for this manuscript.

References