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Catheter Ablation for Atrial Fibrillation

Are Results Maintained at 5 Years of Follow-Up?

Rukshen Weerasooriya, BMEDSC(HONS), MBBS,*† Paul Khairy, MD, PHD,‡ Jean Litalien, MD,* Laurent Macle, MD,‡ Meleze Hocini, MD,* Frederic Sacher, MD,* Nicolas Lellouche, MD,* Sebastien Knecht, MD,* Matthew Wright, PHD, MD,* Isabelle Nault, MD,* Shinsuke Miyazaki, MD,* Christophe Scavee, MD,* Jacques Clementy, MD,* Michel Haissaguerre, MD,* Pierre Jais, MD*

Bordeaux-Pessac, France; Crawley, Western Australia; and Montreal, Quebec, Canada

Objectives This study describes 5-year follow-up results of catheter ablation for atrial fibrillation (AF).

Background Long-term efficacy following catheter ablation of AF remains unknown.

Methods A total of 100 patients (86 men, 14 women), age 55.7 ± 9.6 years, referred to our center for a first AF ablation (63% paroxysmal; 3.5 ± 1.4 prior ineffective antiarrhythmic agents) were followed for 5 years. Complete success was defined as absence of any AF or atrial tachycardia recurrence (clinical or by 24-h Holter monitoring) lasting ≥30 s.

Results Arrhythmia-free survival rates after a single catheter ablation procedure were 40%, 37%, and 29% at 1, 2, and 5 years, respectively, with most recurrences over the first 6 months. Patients with long-standing persistent AF experienced a higher recurrence rate than those with paroxysmal or persistent forms (hazard ratio [HR]: 1.9, 95% confidence interval [CI]: 1.0 to 3.5; $p = 0.0462$). In all, 175 procedures were performed, with a median of 2 per patient. Arrhythmia-free survival following the last catheter ablation procedure was 87%, 81%, and 63% at 1, 2, and 5 years, respectively. Valvular heart disease (HR: 6.0, 95% CI: 2.0 to 17.6; $p = 0.0012$) and nonischemic dilated cardiomyopathy (HR: 34.0, 95% CI: 6.3 to 182.1; $p < 0.0001$) independently predicted recurrences. Major complications (cardiac tamponade requiring drainage) occurred in 3 patients (3%).

Conclusions In selected patients with AF, a catheter ablation strategy with repeat intervention as necessary provides acceptable long-term relief. Although most recurrences transpire over the first 6 to 12 months, a slow but steady decline in arrhythmia-free survival is noted thereafter. (J Am Coll Cardiol 2011;57:160–6) © 2011 by the American College of Cardiology Foundation

Catheter ablation that predominantly targets pulmonary veins (PVs) is well established as a treatment option for patients with symptomatic drug refractory atrial fibrillation (AF), with a steady growth in the number of interventions performed over the past decade (1). Although recent consensus guidelines emphasize the important need for long-term result reporting (1), most studies have limited follow-up to 1 year or less, with few outcome data beyond 3 years. Because the substrate for AF may evolve in a time-dependent fashion, the critically important question arises as to whether ablation simply slows disease progression or confers relatively stable long-term arrhythmia control. Longer-term outcomes are particularly important when one considers that catheter ablation is generally offered to relatively young patients compared with the overall population afflicted with AF. Longer-term outcomes are also highly relevant in modeling and comparing the cost-effectiveness of treatment strategies. We, therefore, sought to assess 5-year outcomes in a cohort of patients with AF ablation at a single center using a uniform approach.

From the *Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, France; †Department of Medicine, University of Western Australia, Crawley, Western Australia; and the ‡Montreal Heart Institute, Montreal, Quebec, Canada. Dr. Macle has received research grant support from Biosense-Webster and St. Jude Medical, and honoraria from Biosense-Webster, Sanofi-Aventis, and St. Jude Medical. Dr. Hocini has received speaker fees from Biosense and Bard. Dr. Nault has received fellowship support from St. Jude Medical. All other authors have reported that they have no relationships to disclose. Oussama M. Wazni, MD, served as Guest Editor for this paper.

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Methods

Patient characteristics. A group of 100 patients who underwent catheter ablation for AF between January 2001 and April

2002 were prospectively followed to determine long-term outcomes. All procedures were performed at Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, using a standard ablation protocol. Inclusion criteria consisted of the following:

1. Age between 18 and 80 years.
2. Symptomatic and/or complicated AF (i.e., stroke, transient ischemic attack, or heart failure).
3. History of documented AF exceeding 6 months. AF was classified as paroxysmal (episodes <7 days) or persistent (>7-day episodes) or long standing persistent (1).
4. Episodes of AF lasting longer than 1 h per week despite a trial of at least 2 antiarrhythmic agents or monotherapy with amiodarone.
5. Provision of patient-informed consent.

Patients with any of the following criteria were excluded from this analysis:

1. Reversible cause for AF (such as hyperthyroidism),
2. Prior AF ablation attempts (surgical- or catheter-based),
3. Residing outside of France,
4. History of AF <6 months,
5. <1 h per week of AF (on average).

Pre-ablation preparation. Antiarrhythmic drugs were discontinued 5 half-lives prior to ablation, except for amiodarone, which was discontinued the preceding week. All patients received oral anticoagulation with warfarin for a minimum of 1 month before ablation, targeting international normalized ratio levels between 2 and 3. Warfarin was discontinued 5 days before ablation and substituted by subcutaneous enoxaparin (1.5 mg/kg twice daily). Transesophageal echocardiography was performed within 4 days of ablation to exclude left atrial thrombi.

Catheter ablation procedure. PROCEDURAL CHARACTERISTICS. All procedures were performed with local anesthesia under conscious sedation, administered by the anesthesia service. Noninvasive blood pressure monitoring and continuous digital pulse oximetry were performed throughout the procedure.

Three vascular sheaths (i.e., 6-, 7-, and 8-F) were inserted in the right femoral vein under lidocaine local anesthesia. A steerable quadripolar catheter (2-5-2 mm, Xtrem, ELA Medical, Montrouge, France) was positioned in the coronary sinus. The 8-F sheath was upgraded to a long sheath (Preface 62 cm, Biosense-Webster, Diamond-Bar, California). Transseptal puncture was performed using a standard needle (Adult BRK 71 cm, St. Jude Medical, St. Paul, Minnesota) by means of a 2-in-1 technique. An ablation catheter (Thermocool D curve 5-mm tip, Biosense-Webster) was subsequently advanced to the left atrium. Contrast hand injection of all PVs was performed in the fluoroscopic anteroposterior projection using a multipurpose catheter (N.I.H., Cordis Corp., Bridgewater, New Jersey). In order to map PV potentials, a fixed diameter (20 mm) steerable decapolar circumferential catheter (Lasso, Biosense-Webster) was advanced via the long sheath.

Abbreviations and Acronyms

AF = atrial fibrillation

PV = pulmonary vein

Surface electrocardiograms and bipolar intracardiac electrograms were continuously monitored using the LabSystem Pro (Bard Electrophysiology, Lowell, Massachusetts). Signals were sampled at 1 kHz, filtered at 0.1 to 100 Hz for surface electrocardiograms and at 30 to 250 Hz for intracardiac signals, and displayed at an amplification of 0.1 mV/cm.

CATHETER ABLATION. All segmental ostial PVs were systematically isolated and the cavotricuspid isthmus was ablated in every patient. Left atrial linear ablation of the roof and mitral isthmus was generally reserved for patients with persistent or long-standing persistent AF, those in whom AF continued despite PV isolation, and recurrent cases. Ablation techniques have been previously described (2–4). Briefly, radiofrequency energy was delivered at the PV ostium using a Cordis-Stockert generator at a temperature setting of 50°C, with a power limit of 30 W for the right superior PV, left superior PV, and right inferior PV, and 25 W for the left inferior PV due to the higher reported incidence of stenosis. Normal saline (0.9%) was infused through the ablation catheter at a pump rate of 2 ml/min during mapping and 10 to 60 ml/min during radiofrequency delivery. Ablation end points consisted of complete elimination or dissociation of PV potentials and bidirectional linear block.

POST-OPERATIVE CARE. Patients were hospitalized for 3 days following catheter ablation, with continuous rhythm monitoring. The day after the intervention, all patients had transthoracic echocardiography to exclude a pericardial effusion or other detectable complications. Oral anticoagulation was reinstituted the day after ablation and subcutaneous heparin injections were continued until international normalized ratio levels exceeded 2. All patients were treated with warfarin for at least 1 to 3 months after ablation. Following this, anticoagulation requirements were individualized. Anticoagulants were generally discontinued in patients deemed recurrence-free and with no other indications for anticoagulation such as prosthetic valves, ischemic stroke, or transient ischemic attack, or other thromboembolic events. In case of recurrent AF, warfarin was reintroduced in preparation for a repeat procedure and/or if clinically indicated. In the absence of arrhythmia recurrence during this initial surveillance period, antiarrhythmic drugs were not represcribed. In the event of early AF recurrence, patients with and without structural heart disease received amiodarone (100 to 200 mg daily) or flecainide (100 to 300 mg daily), respectively. Bisoprolol (2.5 to 5 mg) was prescribed to patients with sinus tachycardia following ablation. Antiarrhythmic agents were discontinued after 1 month if the patient was able to maintain sinus rhythm.

Follow-up. Over the first year, follow-up appointments were systematically scheduled at 1, 3, 6, and 12 months.

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During each such visit, patients were hospitalized for the following investigations: 24-h Holter monitoring, transthoracic echocardiography, and exercise stress testing. Between visits, all patients were encouraged to seek 12-lead electrocardiographic documentation for any symptoms suggestive of AF. If AF recurrence was observed, the patient was offered reablation. Atrial tachycardia and atrial flutter were classified as ablation failure. After a minimum of 5 years following the first catheter ablation procedure, patients were readmitted to hospital to undergo 24-h Holter monitoring, transthoracic echocardiography, and exercise stress testing, and a standard questionnaire was administered (Online Appendix). Success was defined as the absence of symptoms or episodes of AF/atrial tachycardia or flutter greater than 30 s duration off antiarrhythmic agents.

Statistical analysis. Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean ± SD or median and interquartile range (IQR) (25th, 75th percentile) depending on normality of distribution. Time to recurrence and event-free survival curves were estimated by the Kaplan-Meier product-limit method. Univariate and multivariate predictors of recurrent AF following the first and final catheter ablation procedures were assessed in Cox regression models, after verifying proportionality assumptions. Candidate variables with p values <0.20 in univariate analyses were considered in multivariate stepwise regression models. Two-tailed p values <0.05 were considered statistically significant. Analyses were performed with SAS software (version 9.1, SAS Institute, Cary, North Carolina).

Table 1 Baseline Characteristics (n = 100)

Demographic variables	
Age at inclusion, yrs	55.7 ± 9.6
Male sex, %	86
Medical history	
Type of atrial fibrillation, %	
Paroxysmal	64
Persistent	22
Long-standing persistent	14
History of atrial fibrillation, months	72 ± 54
Structural heart disease, %	36
Ischemic	8
Left ventricular hypertrophy	16
Valvular heart disease	5
Idiopathic dilated cardiomyopathy	7
Left ventricular ejection fraction, %	70 ± 11
Risk factors for thromboembolism, %	
Hypertension	43
Diabetes	3
Congestive cardiac failure	9
Prior thromboembolic event	9
Prior stroke	8
CHADS2 score, %	
0	48
1	32
≥2	20
Medical therapy	
Number of ineffective antiarrhythmic drugs	3.5 ± 1.4
Failed amiodarone therapy, %	67
Major amiodarone-related complication, %	10

CHADS2 = Congestive heart failure, Hypertension, Age >75, Diabetes, prior Stroke or TIA.

Results

Baseline and procedural characteristics. During the study period, 552 patients underwent ablation for AF at our center. Patients followed outside of France were excluded (n = 64), as were those with prior ablation (n = 256), <1 h of AF per week on average (n = 98), and a history of AF <6 months (n = 34). The study cohort consists of the remaining 100 patients, 86% men, age 55.7 ± 9.6 years.

Baseline characteristics are summarized in Table 1. Seven patients had idiopathic dilated cardiomyopathy defined as dilation and systolic ventricular dysfunction in the absence of congenital, valvular, coronary artery, or any systemic disease known to cause myocardial dysfunction. Valvular heart disease was defined as stenosis or regurgitation of any heart valve greater than "mild" by echocardiographic criteria.

In all, 175 procedures were performed, with a median of 2 (IQR: 1, 2) per patient as follows: 49 had 1, 34 had 2, 13 had 3, and 4 had 4 to 7 interventions. Figure 1 provides an overview of recurrences and repeat interventions. The predominant indication for a repeat procedure was AF in 45 (60%) and other atrial tachyarrhythmias in 30 (40%) patients. Even though all patients had PV isolation and cavotricuspid isthmus ablation, left atrial linear ablation was performed in 92 patients and consisted of left isthmus ablation in 89 (70 during the first procedure) and/or roofline ablation in 13 (5 during the first procedure). At the time of the first procedure, 32 patients were on amiodarone; at repeat procedures, 6 patients were on amiodarone.

Follow-up. Patients were followed for a median of 60 (IQR: 56, 62) months from the first procedure and 54 (IQR: 51, 60) months from the last procedure. Three deaths occurred over the course of follow-up, none deemed cardiac in origin (lung cancer, n = 1; cerebral hematoma in an anticoagulated patient at 17 months after ablation, n = 1; and suicide, n = 1).

Arrhythmia-free survival after a single procedure. Actuarial arrhythmia-free survival rates after a single catheter ablation procedure were 39.8 ± 5.1%, 36.5 ± 5.0%, and 28.5 ± 4.7% at 1, 2, and 5 years, respectively. As shown in Figure 2, most recurrences occurred during the first 6 months, with an actuarial event-free survival rate of 44.2 ± 5.1%. After a single procedure, the only univariate predictor of recurrence was type of AF, with long-standing persistent AF associated with a hazard ratio (HR) of 1.9, 95% confidence interval (CI): 1.0 to 3.5, p = 0.0462, when compared with paroxysmal or persistent forms.

Arrhythmias recurred in 10 of 36 (28%) patients who had maintained sinus rhythm for at least 1 year. Of the 68 patients with recurrent arrhythmias, 17 did not have repeat

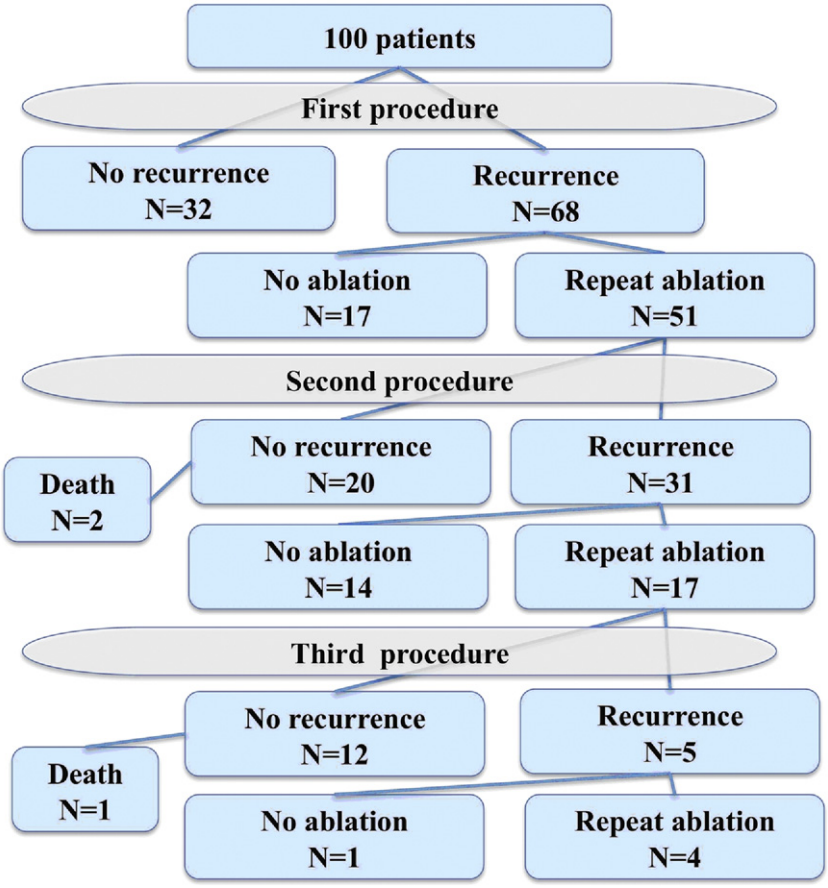

Figure 1 **Study Flow Chart**

Flow-chart delineating recurrences and repeat interventions.

interventions for the following reasons: spontaneous or antiarrhythmic-mediated resolution of symptoms (n = 7), patient refusal (n = 3), infrequent and/or mild residual symptoms (n = 6), and morbid obesity (n = 1). In all except 3 cases of purely asymptomatic AF recurrence, recurrence was symptomatic at least some of the time. Fifty-one patients underwent repeat procedures targeting PV conduction recovery in all and gaps in linear lesions in 28 patients.

Arrhythmia-free survival since last intervention. Actuarial arrhythmia-free survival rates following the last catheter ablation procedure were 87.1 ± 3.5%, 81.4 ± 4.1%, and 62.9 ± 5.4% at 1, 2, and 5 years, respectively. Of the 77 patients who were arrhythmia-free at 1 year of follow-up, 19 (25%) presented with a later recurrence. In the 7 patients with repeat interventions (5 for AF; 2 for left atrial flutter), the following nonexclusive observations were noted: PV reconnection (n = 6), linear lesion gap (n = 4), non-PV foci (n = 3), and left atrial flutter without previous linear ablation (n = 1). Multiple substrates for recurrence were identified in all but 2 patients (non-PV foci in 1 patient; PV reconnection in 1 patient).

Figure 3 displays the slow but steady decline in arrhythmia-free survival corresponding to an average actuarial event rate of 8.9% per year. Univariate predictors of recurrence were long-standing persistent AF (HR: 2.6, 95% CI: 1.1 to 6.0; p = 0.0319), presence of valvular heart disease (HR: 5.2, 95% CI: 1.8 to 15.2; p = 0.0026), and nonischemic dilated cardiomyopathy (HR: 26.8, 95% CI: 5.1 to 140.1; p < 0.0001). Valvular heart disease (HR: 6.0, 95% CI: 2.0 to 17.6; p = 0.0012) and nonischemic dilated cardiomyopathy (HR: 34.0, 95% CI: 6.3 to 182.1; p < 0.0001) remained independent predictors of recurrent AF in multivariate analyses. The 64 patients with paroxysmal AF at baseline did not progress to persistent or permanent AF during the course of the study follow-up.

Complications. There were no procedure-related deaths. Complications were as follows: cardiac tamponade (surgical intervention, n = 3), pericardial effusion managed conservatively (n = 3), asymptomatic 70% PV stenosis (n = 1), arteriovenous femoral fistulae (n = 1), femoral false aneurysm (n = 1), anaphylactic shock secondary to propofol administration (n = 1), and ventricular fibrillation second-

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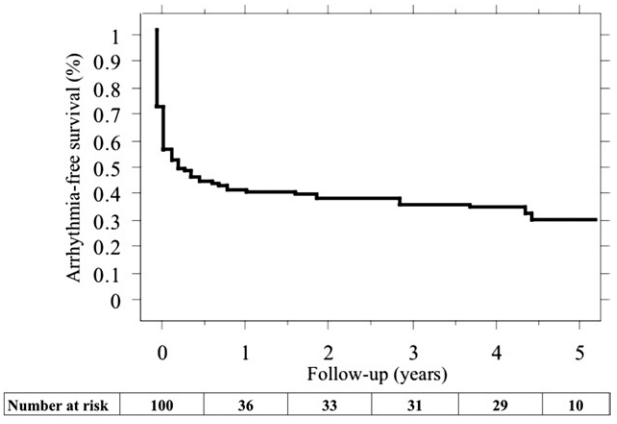

Figure 2 **Single Procedure Success**

Kaplan-Meier event-free survival curve after a single catheter ablation attempt.

ary to intraprocedural direct current cardioversion (n = 1). No late or unexpected complications were detected at 5-year follow-up.

Discussion

Herein, we report the longest follow-up to date of any percutaneous AF procedure. By 5 years of follow-up, freedom from recurrent AF was 63%, albeit with repeat interventions in 51%. Moreover, we observed a gradual attrition in arrhythmia-free survival, with an 8.9% annual recurrence rate following the last ablation attempt. Notably, the long-term effectiveness of a single procedure was modest, with 29% arrhythmia-free survival at 5 years. No new or unforeseen sequelae of catheter ablation were detected beyond periprocedural complications, with no thromboembolic events or clinically significant PV stenosis. These results have implications for the long-term follow-up of patients after radiofrequency catheter ablation for AF.

The long-term success rates in our study are consistent with prior reports of 70% at 20 months (5) and 66% at 26 months (6) and an 8.7% long-term recurrence rate at 28 months described by Shah et al. (7). In further extending the follow-up period, we noted that the rate of decline in freedom from AF after the first intervention stabilized after the initial 12 months, although it did not entirely plateau. Clinical implications of these results are substantial with regard to the care of patients with AF. Firstly, empirical long-term follow-up data should be presented to patients to inform the decision-making process and provide reasonable expectations. Secondly, ongoing surveillance is warranted, even if catheter ablation was deemed initially successful. In accordance with the recently published consensus statement (1), patients with a previous history of stroke should not discontinue anticoagulation therapy.

Late recurrences and frequent reinterventions should also be factored into cost-modeling assessments, as these procedures become more widely performed and increasingly influence overall health care expenditure. Although prior studies have concluded that the net benefit of catheter ablation over medical therapy extends to approximately 5 years (8,9), projected costs have not considered later (i.e., >3 years) recurrences and reinterventions. For example, Khaykin et al. (9) assumed a maximum 5% late recurrence rate, which underestimates results from our long-term findings. Given that patients in this study were relatively young, with an average age of 55 years at entry, extending follow-up even further would be of interest in determining the likelihood of AF recurrence over a lifespan.

Patients had a median of 2.0 procedures, reflecting a treatment strategy favoring early reintervention for recurrences (10). The high rate of repeat procedures accounts, in part, for the marked disparity between event-free survival rates following single and final interventions. The benefit of repeat interventions is partly captured by the difference between these actuarial event rates. Need for repeat interventions and recurrent arrhythmias were modulated by type of AF at baseline, with long-standing persistent AF being a univariate predictor of recurrence. Despite the clinical observation that persistent AF cases are more difficult to treat and require a higher number of procedures (11,12), type of AF was not a predictor of outcome in the multivariate analysis.

Importantly, our study population was not representative of patients with AF at large, as it consisted predominantly of younger, healthier, nonobese patients with relatively smaller atria and paroxysmal or recent progression to persistent AF.

Electrophysiological mechanisms underlying early recurrences following PV isolation have been extensively studied. In recurrences <3 months after ablation, Gerstenfeld et al. (13) found that 61% of PVs had recovered conduction. Callans et al. (14) reported that PV reconnection accounted for 77% of recurrences. Extending the follow-up to 12 months, Mainigi et al. (15) found that 75% of implicated

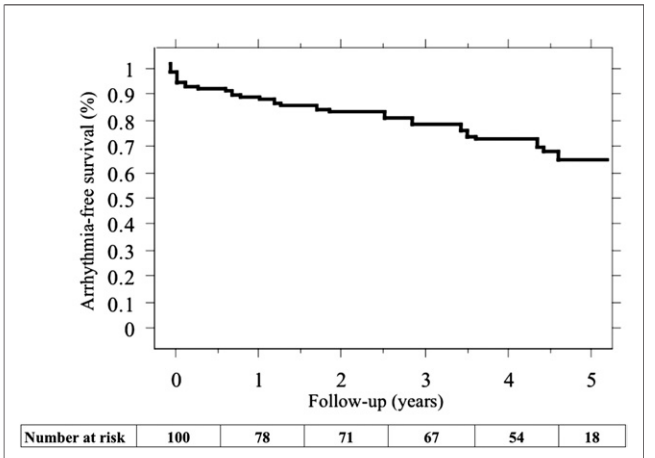

Figure 3 **Multiple Procedure Success**

Kaplan-Meier event-free survival curve after the last catheter ablation attempt.

foci were within PVs, although 30% had not been previously targeted. Notably, Hsieh et al. (16) reported that PV foci were less likely to be responsible for recurrences beyond 12 months. Using a segmental PV isolation technique, Solheim et al. (6) noted recurrences >12 months (mean 26 ± 11 months) in 8 of 187 (4%) patients with paroxysmal AF, whereas Cheema et al. (17) reported a success rate of 69% at 26 ± 11 months in a subgroup with paroxysmal AF considered "ideal" candidates for PV isolation. In our series, only 7 of 31 patients with recurrences after 12 months were restudied and most (i.e., 6 patients) had PV reconnection. Minimizing the likelihood of PV reconnection appears, therefore, to be a worthy objective. Some investigators have suggested that propensity for PV reconnection may be assessed acutely by administering an adenosine bolus (18) or retesting 30 and 60 min after ablation (19). Techniques to achieve optimal safety and efficiency remain in evolution, including different energy modalities, delivery platforms, and novel biological solutions.

Late recurrences of AF may reflect dynamic alterations in the underlying substrate as well as the impact of associated diseases such as hypertension, sleep apnea, and diabetes on natural history of AF. Antifibrotic and antifibrillatory effects of nonantiarrhythmic drugs such as angiotensin-converting enzyme and angiotensin 2 inhibitors are increasingly appreciated and may potentially improve long-term outcomes by preventing such remodeling (20,21). The side-effect profile of these agents is also attractive in comparison to antiarrhythmic drugs. Nevertheless, although these agents may hold promise, supporting evidence from clinical research is required before routinely adopting these treatment strategies. Although our study did not particularly target preventive measures, previous studies suggest that long-term benefit may be derived from careful efforts to control hypertension and sleep apnea, and avoidance of weight gain (22–24).

Study limitations. These results may not be generalized as they were observed in a single, relatively high volume "early developer" experience. Monitoring for AF recurrence in this earlier cohort of patients was not as extensive as recommended by the recently published consensus statement. The potential for under-recognition of silent AF therefore exists. However, because AF ablation in this patient cohort was performed for symptomatic control, symptomatic AF recurrence remains a clinically valid end point. Study conclusions must be interpreted in light of this caveat. Under-recognition of silent AF should, however, heighten concerns for eliminating long-term anticoagulation among those at risk.

Similarly, computed tomography scanning or magnetic resonance imaging was not routinely performed at the end of the 5-year follow-up to detect asymptomatic PV stenosis, although patients were specifically questioned with regard to PV stenosis symptoms and imaging was performed to rule out a suspected diagnosis.

Furthermore, the approach to AF ablation has changed from an ostial or segmental approach to a more circumferential approach and the procedure used nowadays consisting of a larger encircling of the ipsilateral veins has been shown to be more effective. As a consequence, we suspect that the success rate reported here is at least equal if not better using current techniques.

Conclusions

In selected patients with AF, a catheter ablation strategy with repeat intervention as necessary provides acceptable long-term relief from symptomatic recurrences. Although most recurrences transpire over the first 6 to 12 months, a slow but steady decline in arrhythmia-free survival is noted thereafter, even after 3 or more years of apparent arrhythmia control. Such long-term follow-up data should be openly discussed with patients, factored into management decisions, and incorporated into cost-effectiveness models that assess the merits of an ablation approach.

Reprint requests and correspondence: Dr. Rukshen Weerasooriya, Hôpital Cardiologique du Haut-Lévêque, 33604 Bordeaux-Pessac, France. E-mail: rukshen@afablationclinic.com.au.

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Key Words: ablation ■ atrial fibrillation ■ follow-up.

APPENDIX

For a copy of the questionnaire used during follow-up, please see the online version of this article.