Changes in Atrial Fibrillation Cycle Length and Inducibility During Catheter Ablation and Their Relation to Outcome

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Background—The modification of atrial fibrillation cycle length (AFCL) during catheter ablation in humans has not been evaluated.

Methods and Results—Seventy patients undergoing ablation of prolonged episodes of AF were randomized to pulmonary vein (PV) isolation or additional ablation of the mitral isthmus. Mean AFCL was determined at a distance from the ablated area (coronary sinus) at the following intervals: before ablation, after 2- and 4-PV isolations, and after linear ablation. Inducibility of sustained AF (≥10 minutes) was determined before and after ablation. Spontaneous sustained AF (715±845 minutes) was present in 30 patients and induced in 26 (AFCL, 186±19 ms). PV isolation terminated AF in 75%, with the number of PVs requiring isolation before termination increasing with AF duration ($P=0.018$). PV isolation resulted in progressive or abrupt AFCL prolongation to various extents, depending on the PV: to 214±24 ms ($P<0.0001$) when AF terminated and to 194±19 ms ($P=0.002$) when AF persisted. The increase in AFCL (30±17 versus 14±11 ms; $P=0.005$) and the decrease in fragmentation (30.0±26.8% to 10.3±14.5%; $P<0.0001$) were significantly greater in patients with AF termination. Linear ablation prolonged AFCL, with a greater prolongation in patients with AF termination (44±13 versus 22±23 ms; $P=0.08$). Sustained AF was noninducible in 57% after PV isolation and in 77% after linear ablation. At 7±3 months, 74% with PV isolation and 83% with linear ablation were arrhythmia free without antiarrhythmics, which was significantly associated with noninducibility ($P=0.03$) with a recurrence rate of 38% and 13% in patients with and without inducibility, respectively.

Conclusions—AF ablation results in a decline in AF frequency, with a magnitude correlating with termination of AF and prevention of inducibility that is predictive of subsequent clinical outcome. **(*Circulation*. 2004;109:3007-3013.)**

Key Words: arrhythmia ■ cardioversion ■ drugs ■ electrophysiology ■ surgery

Curing atrial fibrillation (AF) by surgical or catheter ablation is based on the elimination of the initiating triggers and/or the maintaining substrate. Most current techniques target the pulmonary veins (PVs) to isolate these dominant sources of activities while additional substrate modification is optionally used.[1–7] However, whether an individual patient needs additional substrate modification and the extent and type of modification remain unknown.

Experimental mapping studies have shown that the AF cycle length (AFCL) is highly correlated with local refractory periods,[8] shortens with maintenance of AF,[9] and prolongs progressively or immediately before spontaneous or drug-induced termination;[10] the latter has not been consistently observed in humans.[11] These findings have not been previously evaluated during catheter ablation of AF in humans. This prospective clinical study investigates the variation of AFCL during PV isolation and linear ablation performed during ongoing AF, its correlation with inducibility maneuvers, and subsequent clinical outcome.

Methods

Study Population

The study comprised 70 patients with drug-refractory AF undergoing curative ablation. Patients were selected on the basis of episodes of clinical AF persisting for ≥1 hour to minimize the chance of random termination of AF during ablation. All patients underwent initial PV isolation, after which half the group was randomized to additional linear ablation of the mitral isthmus (lateral mitral annulus to the left inferior PV). In addition, cavotricuspid isthmus ablation was performed in all patients. Baseline characteristics of these groups are presented in the Table.

All patients gave written informed consent to the study, which was approved by the institutional Clinical Research and Ethics Committee.

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Baseline Characteristics

	PVI (n=35)	PVI+Mitral Isthmus Ablation (n=35)	P
Male	26	26	NS
Age, y	53±8	53±9	NS
Structural heart disease	18	12	NS
Hypertension	10	7	NS
Failed antiarrhythmics, n	3.1±1.1	3.4±1.1	NS
LV end-diastolic diameter, mm	51±6	53±6	NS
LV end-systolic diameter, mm	32±6	31±6	NS
LV ejection fraction, %	65±11	68±13	NS
LA diameter, mm			
Parasternal	43±6	42±8	NS
Longitudinal	54±6	56±7	NS
Transverse	40±8	43±6	NS

PVI indicates PV isolation; LV, left ventricular; and LA, left atrial.

Electrophysiological Study

All antiarrhythmics, except for amiodarone, were ceased ≥5 half-lives before ablation. Oral anticoagulation was administered (target international normalized ratio, 2 to 3) for at least 1 month before the procedure, and transesophageal echocardiography was performed within 3 days of the procedure to exclude atrial thrombus.

Surface ECG and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Bard Electrophysiology). Intracardiac electrograms were filtered from 30 to 500 Hz.

Radiofrequency Ablation

All patients had PV isolation and cavotricuspid isthmus ablation. Mitral isthmus ablation was performed in 35 patients.

PV Electrical Isolation and Cavotricuspid Isthmus Ablation

The following catheters were introduced via the right femoral vein for electrophysiological study: (1) A steerable quadripolar catheter (5-mm electrode spacing, Xtrem, ELA Medical) was positioned within the coronary sinus (CS) with the proximal electrode positioned at 4 to 5 o'clock along the mitral annulus in left anterior oblique projection; (2) a circumferential mapping catheter (Lasso, Biosense-Webster) was introduced after transseptal access and stabilized with the aid of a long sheath (Preface Multipurpose, Biosense-Webster) that was continuously perfused with heparinized glucose; and (3) a 4-mm irrigated-tip ablation catheter (Celsius Thermocool, Biosense-Webster). After transseptal puncture, a single bolus of 50 IU/kg heparin was administered and repeated only for procedures lasting ≥4 hours.

Ablation of the PVs was begun randomly in either the right or left PVs and performed individually or as a pair when the ostia were coalescent. It was performed 1 cm from the ostium of both right PVs and for the posterior and superior aspects of the left PVs to minimize the risk of PV stenosis. It was started at the posterior wall (fluoroscopically facing the border of the spine) and continued around the venous perimeter. When ablation was required at the anterior portions of the left PVs, energy had to be delivered within the first millimeters of the vein (rather than the posterior wall of appendage) to achieve effective disconnection. Radiofrequency energy was delivered for 30 seconds at each point; this application was prolonged for 1 to 2 minutes when a change in morphology or in the sequence of the PV potentials occurred as determined by circumferential mapping. The procedural end point was total elimination or dissociation of the PV potentials. Additional ostial applications were performed after PV isolation to eliminate all ostial PV potentials to reduce the risk of recurrence caused by ostial foci. Radiofrequency energy was delivered with power limited to 30 (inside) and 40 W (outside the PV) using irrigation rates of 5 to 20 mL/min (0.9% saline via Cool Flow, Biosense-Webster) to achieve the desired power delivery. Temperature was limited to 50°C.

Cavotricuspid isthmus ablation was performed in all patients with the end point of bidirectional conduction block. Radiofrequency energy was delivered with power limited to 40 W using irrigation rates of 5 to 20 mL/min to achieve the desired power delivery. Temperature was limited to 50°C.

Mitral Isthmus Ablation

In patients randomized to left atrial linear ablation, mitral isthmus ablation was performed between the left inferior PV (and contiguous root of the appendage) and the lateral mitral annulus. Radiofrequency energy was delivered endocardially using power limited to 40 W and epicardially through the CS (when needed) with a power of 25 to 30 W. Irrigation rates of up to 60 mL/min were used as required. Temperature was limited to 50°C. The end point of ablation was bidirectional conduction block at the mitral isthmus.

Study Protocol

Induction of Atrial Fibrillation

The inducibility and duration of AF were determined at the following predetermined intervals: (1) before ablation, (2) after isolation of all PVs, and (3) after mitral isthmus ablation in those randomized to this arm of the study. For the purposes of the study, patients presenting in AF at the time of their procedure were considered inducible before ablation.

In the initial 15 patients, AF inducibility was evaluated first by programmed extrastimuli using single and double extrastimuli at twice diastolic threshold and then by burst atrial pacing (5-second bursts at an output of 20 mA) from the mid CS and right atrial free wall beginning at a cycle length of 250 ms and reducing by 10-ms intervals until atrial refractoriness. Of the initial 15 patients, only 8 were inducible by programmed extrastimuli, whereas all were inducible by burst pacing. To reliably induce AF while minimizing the procedural and study duration, the latter protocol of induction was used in the rest of the study.

AF was considered inducible if it persisted for ≥1 minute and sustained if it persisted for ≥10 minutes. If AF terminated after <1 minute, induction was repeated at least 3 times from each site. In all cases, ablation was begun after induced AF was observed for at least 10 minutes. If AF became sustained, ablation was performed during AF without cardioversion, and the duration of AF was noted.

AF was defined by the beat-to-beat variability in cycle length and morphology; atrial flutter was defined as a rapid regular atrial rhythm with stable cycle length, morphology, and activation sequence. A macroreentrant mechanism was defined by mapping of the entire cycle length and entrainment mapping demonstrating a postpacing interval of <30 ms in the right or left atrium.

Atrial Fibrillation Cycle Length

The AFCL and percentage electrogram fragmentation were determined within the CS (1) before ablation, (2) after isolation of 2 and all PVs, and (3) after mitral isthmus ablation in those randomized to this arm of the study. If AF terminated during ablation, directly to sinus rhythm or by conversion to flutter, the AFCL was determined before termination.[9,12] Its variability was determined by the difference between the maximum and minimum of 3 such measurements before ablation was begun. Interelectrogram intervals of <100 ms and continuous electrical activity were defined as fragmented and counted as a single interval.[13,14] When such fragmented regions persisted for >70% of the evaluated segment, the AFCL was excluded from analysis. The percentage of fragmentation was determined by expressing the fragmented duration as a function of the total duration evaluated. In addition, when AF terminated during PV ablation, the cycle length at that PV was evaluated before ablation and before termination.

The AFCL was measured manually with online calipers at a paper speed of 100 mm/s by averaging 30 consecutive cycles. To avoid transitional cycle lengths, these parameters were determined at least 1 minute after the onset of AF and 10 cycles before the termination of AF.

Follow-Up

After ablation, patients received subcutaneous heparin while oral anticoagulation was reinitiated. All patients had at least 3 days of ambulatory monitoring in hospital during this time. In the absence of concurrent indications, all antiarrhythmic drugs were stopped after ablation.

Patients were hospitalized for 1 day at 1, 3, 6, and 12 months after the last procedure for assessment involving transthoracic echocardiography, ambulatory monitoring, and stress testing. At 12 months after the procedure, all patients underwent CT angiography to exclude PV stenosis. If patients maintained sinus rhythm for 3 months, anticoagulation was stopped. In the event of early recurrence of AF, patients were offered further ablation during the index hospitalization or trial of antiarrhythmics for 1 month. A successful outcome was defined as the absence of arrhythmia (AF or flutter) beyond the first month without the use of antiarrhythmics.

Statistical Analysis

All variables are reported as mean±SD. Comparison between groups was performed with either Student's *t* test or the Wilcoxon rank-sum test. Categorical variables were compared by use of Fisher's exact test. Sequential data measurements were analyzed by repeated-measures ANOVA, followed by post hoc analysis with Fisher's least significant difference procedure. A Kaplan-Meier analysis with log-rank test was used to determine the probability of freedom from recurrent AF. Statistical significance was established at $P<0.05$.

Results

These patients had AF for 61±51 months and failed 3.3±1.1 antiarrhythmics before ablation, and 43% had structural heart disease. There were no significant differences in baseline clinical or echocardiographic characteristics between the 2 groups (the Table).

PV isolation was achieved in all cases using 36±11 minutes of radiofrequency energy applications taking 70±21 minutes. Mitral isthmus ablation was performed using an additional 22±11 minutes of radiofrequency energy applications. The procedure and fluoroscopic durations were 132±53 and 34±17 minutes, respectively, for PV isolation and 155±52 and 44±26 minutes when mitral isthmus ablation was also performed. There were no significant complications associated with the ablation procedure.

At the beginning of the ablation procedure, spontaneous AF was present in 30 patients (43%) for 715±845 minutes. In the 40 remaining patients, burst pacing induced AF in 32 (80%), 24 from the CS and 8 from the right atrium, and AF became sustained in 26 patients. The mean AFCL in the CS before ablation was 186±19 ms, with a variability of 8.5±4.6 ms.

Effect of PV Isolation on Atrial Fibrillation

Of the patients in sustained AF, PV isolation was observed to terminate AF in 42 of 56 patients (75%), either directly in sinus rhythm (31; Figure 1) or by organizing to atrial flutter (right side in 8, left side in 3). This occurred after ablation of 1, 2, 3, or 4 PVs in 10 (17.8%), 6 (10.7%), 11 (19.6%), and 13 (23.2%), respectively (Figure 2). AF termination occurred with disconnection in 4 and before the targeted PV was totally disconnected in 36; however, there was dramatic slowing of PV activity before termination in all patients (cycle length, 175±19 to 251±36 ms; $P<0.0001$). Additional ostial applications after PV isolation interrupted AF in 2 patients (3.6%), whereas it did not terminate AF in remaining 14. The initial duration of AF was found to demonstrate a significant relationship with the number of PVs requiring isolation to achieve termination of AF (Figure 2; $P=0.018$).

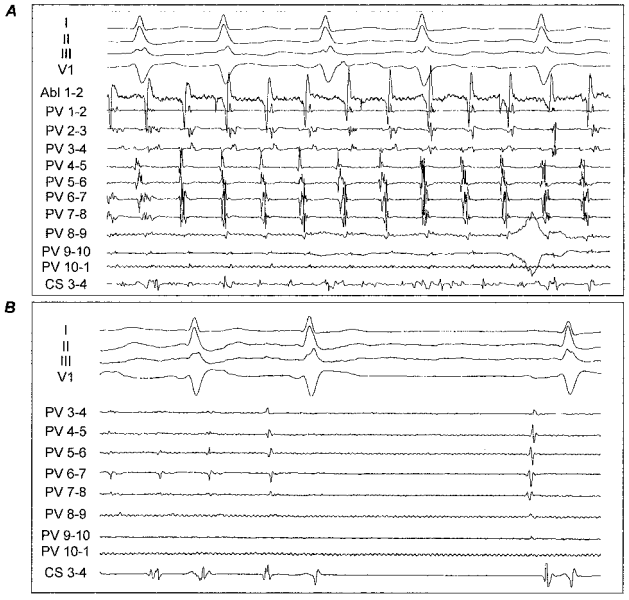

Figure 1. A, Ablation (facing poles 8 to 10) of right superior PV with fragmented and short AFCL seen within CS. B, Termination of AF (duration, 47 minutes) occurred after prolongation of AFCL within CS. Although targeted PV remains connected, AF termination was preceded by dramatic slowing of PV activity (CL, from 160 to 215 ms).

PV isolation resulted in a gradual and progressive increase in the AFCL, with only 6 patients demonstrating an increase of ≤5 ms. This increase was observed to a varying extent in each patient and between PVs. Although some PV ablations did not change the AFCL, a jump in the AFCL was observed with others (Figure 3). There was a significant increase in AFCL in patients in whom AF terminated during ablation

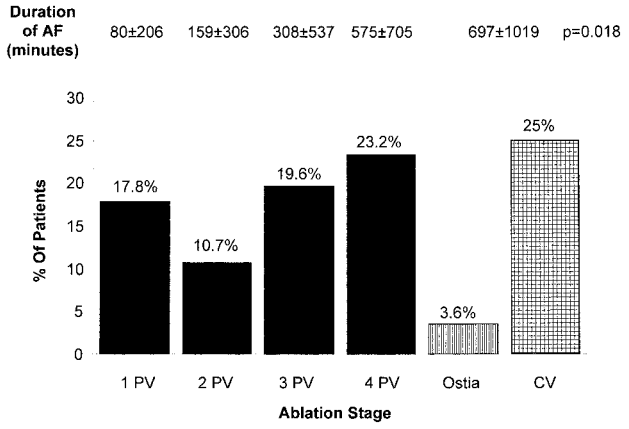

Figure 2. Termination of sustained AF with PV ablation.

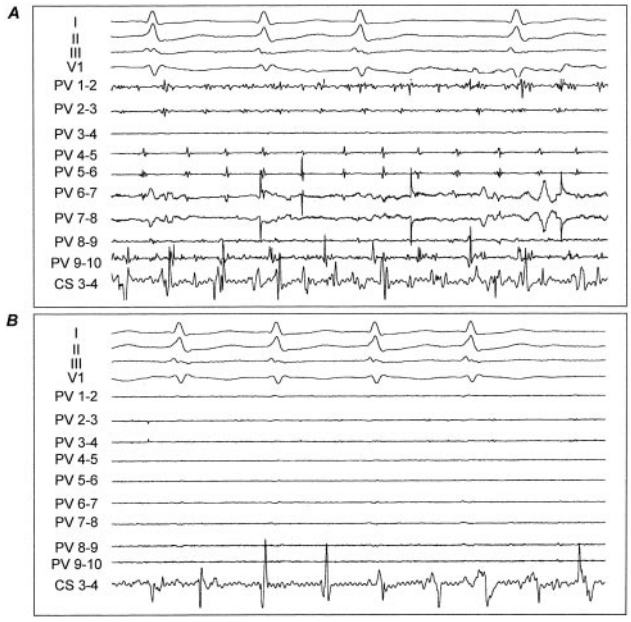

Figure 3. Ablation of right superior PV. A, PV potentials before ablation with CS showing fragmented and rapid activity (AFCL, 164 ms). B, After isolation, AFCL (208 ms) in CS is obviously prolonged.

(184±19 to 214±24 ms; $P<0.0001$) and to a lesser extent in patients with persistent AF after PV ablation (180±20 to 194±19 ms; $P=0.002$; Figure 4). This cumulative increase with ablation was similar whether conversion occurred to sinus rhythm or atrial flutter. It resulted in a significantly increased gradient of AFCL in patients in whom AF terminated (Figure 4) compared with those with persistent AF after PV ablation (30±17 versus 14±11 ms; $P=0.005$). In addition, these patients demonstrated a significant reduction in fragmentation (30.0±26.8% to 10.3±14.5%; $P<0.0001$) compared with those in whom AF persisted despite ablation (49.1±38.3% to 40.9±30.8%; P=NS). There was no relationship between the duration of radiofrequency energy delivery and the cumulative prolongation of the AFCL (P=NS).

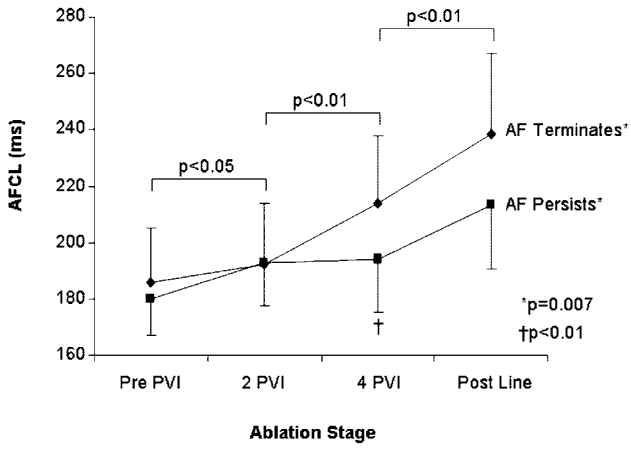

Figure 4. AFCL in CS with ablation. Demonstrated is AFCL at each time point in patients with and without AF termination during ablation.

Patients with structural heart disease demonstrated a similar increase in the AFCL with PV ablation from 183±19 to 205±24 ms ($P<0.0001$). This increase was significantly greater in patients in whom AF terminated during ablation (183±17 to 211±25 ms) compared with those with persistent AF (183±15 to 194±20 ms), representing an increase of 28±17 versus 11±8 ms ($P=0.02$), respectively.

The increase in AFCL was also observed in patients using amiodarone, from 190±20 to 207±25 ms ($P=0.009$) with PV ablation, with a trend toward a greater increase in the AFCL in patients in whom AF terminated [22±14 (n=10) versus 9±17 (n=6) ms; $P=0.15$].

After PV isolation, sustained arrhythmia persisted or could be induced in 30 patients (43%). The cumulative increase in the AFCL was greater in patients in whom AF could not be induced compared with those with inducible sustained arrhythmia (33±15 versus 20±17 ms; $P=0.015$). There was no relationship between the duration of RF delivery and persistent inducibility.

The following variables were demonstrated to be predictive of noninducibility after PV ablation: smaller left atrial transverse ($P=0.048$) and longitudinal ($P=0.05$) diameters, greater increase in AFCL ($P=0.046$), and termination of AF during PV ablation ($P=0.001$).

Effect of Additional Linear Ablation

In the 35 patients randomly assigned to undergo additional mitral isthmus ablation, 14 patients (40%) had persistent or inducible sustained arrhythmia (11 AF, 3 left atrial flutter) after PV isolation. AF terminated spontaneously before the beginning of ablation in 3 patients and terminated during ablation in 4, and the remaining 4 required electrical cardioversion. The AFCL prolonged (Figure 5) further in patients in whom AF terminated during ablation compared with those with persisting AF (44±13 versus 22±23 ms; $P=0.08$; Figure 4).

Additional ablation was performed, targeting the gaps after the resumption of sinus rhythm to achieve bidirectional linear block in 33 patients. After ablation, the inducibility of sustained arrhythmia was evaluated in all patients, with 8 (23%) being inducible (AF in 5, left atrial flutter in 3) and 27 (77%) being noninducible.

Left Atrial Flutter During Ablation of Atrial Fibrillation

During PV ablation in patients with AF, conversion to left atrial flutter was observed spontaneously in 3 patients. Another 6 patients had left atrial flutters induced by burst pacing after PV ablation. Mapping of these flutters demonstrated macroreentry around the right PVs (n=4) or perimitrally (n=3); in 2 patients, atrial flutter terminated during entrainment and could not be mapped. All 3 patients with spontaneous atrial flutter underwent radiofrequency ablation of the roofline (left superior PV to the right superior PV), interrupting atrial flutter in 1 patient and changing the circuit to perimitral in 2 patients, necessitating ablation of the mitral isthmus.

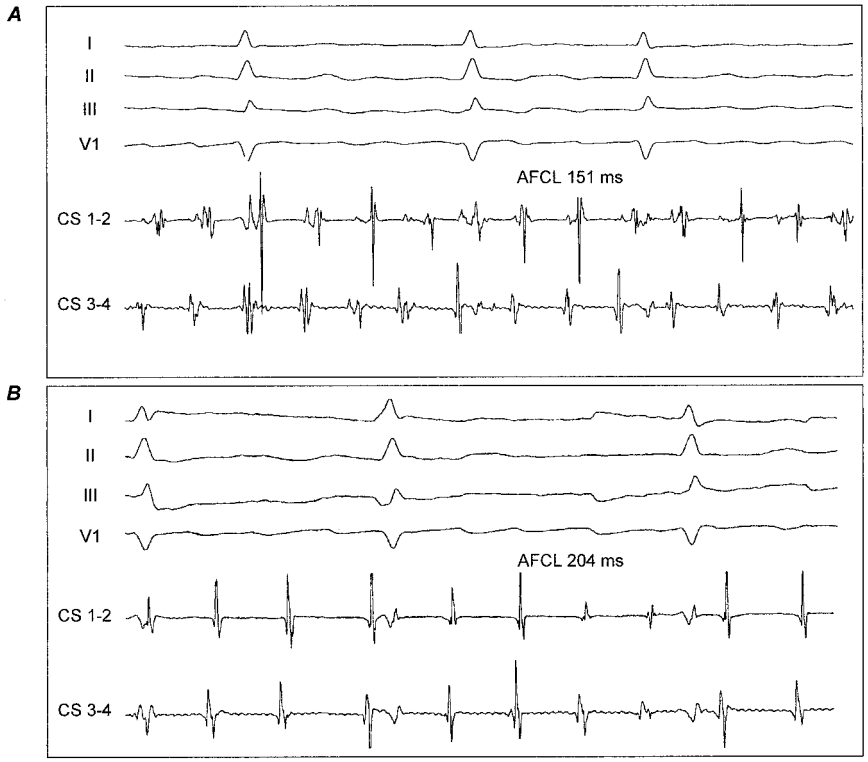

Figure 5. AFCL in CS before and after ablation of mitral isthmus. A, AFCL of 151 ms, which remains short despite isolation of all 4 PVs. B, Strikingly prolonged AFCL (gradient, 53 ms) after linear ablation.

Follow-Up

In the 3 days after ablation, 9 patients (13%) underwent reablation for early recurrence of AF. Focal ablation was performed for ≥1 non-PV foci, triggering AF in 7 patients (2 in right atrium, 2 in the superior vena cava, 2 in the posterior left atrium, 1 in the left septal, and 1 in the CS ostium), PV ostial foci in 5, recovery of PV conduction in 3, and a gap in the mitral isthmus line in 1.

At 7±3 months of follow-up, 26 patients (74%) with PV isolation and 29 patients (83%) with additional mitral isthmus ablation were arrhythmia free without the use of antiarrhythmics. Of the 15 patients who had recurrent atrial arrhythmia, 4 had left atrial flutter and 11 had AF.

Noninducibility of AF after ablation was associated with the long-term clinical suppression of arrhythmia, with 40 of the 46 patients (87%) who were noninducible after the ablation procedure remaining arrhythmia free without the use of antiarrhythmics (compared with 15 of 24 patients; $P=0.03$; Figure 6). Eleven of the 15 patients with recurrent arrythmia underwent an additional procedure. The 3 previously noninducible patients showed PV recovery as compared with 4 of the 8 patients with persistent inducibility.

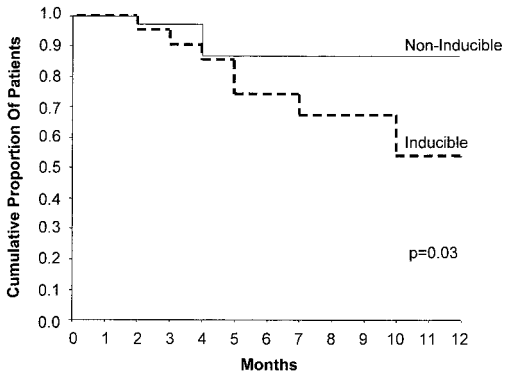

Figure 6. Freedom from recurrent AF in patients with and without the inducibility of AF at end of ablation procedure.

Discussion

This study demonstrates that PV isolation and additional linear ablation produce a progressive and cumulative increase in AFCL, with the magnitude of increase correlating with the termination of AF and prevention of its reinduction associated with subsequent clinical outcome.

Role of the PVs in Maintaining AF

In the present study, prolongation of AFCL within the CS was observed during PV ablation and increased gradually with the number of ablated PVs, varying in degree from vein to vein and ranging from being imperceptible in some to an obvious jump in others. This was associated with a decrease in the degree of fragmentation and the termination of AF by either the resumption of sinus rhythm or conversion to atrial flutter. Longer episodes of AF required a greater number of PVs to be ablated for AF termination than short episodes. In addition, linear ablation at the mitral isthmus after PV isolation produced further prolongation of the AFCL, however to a variable amount.

This decline in AF frequency produced by PV isolation confirms the participation of PV activity in the maintenance of AF by the progressive slowing/extinguishing of "perpetuating activities," with this term used in a broad sense. This phenomenon was observed whether AF occurred spontaneously (even for long duration) or required artificial induction, providing direct evidence for the role of the PVs in maintain-

ing AF previously suggested by observations of sustained[15] or intermittent bursts of activity from the PVs[16–18] with a distal-to-proximal activation.[19] Such a perpetuating role has also been suggested in chronic AF during surgical mapping, with rapid activity emanating from the PV region continuously, intermittently, or alternately.[20] This region has been demonstrated to be capable of sustaining both focal and reentrant sources of activity, which are favored by short local refractory periods and prolonged anisotropic conduction associated with the PVs.[12,20–25]

PV isolation produced not only prolongation of AFCL but termination of AF in 75% of patients, which seems analogous to that observed during pharmacological cardioversion in which AFCL increased with the fusion or reduction of wavelets meandering throughout the atria.[10] Our results indicate that activity perpetuating AF emanates from the PV regions in a subset of patients with paroxysmal AF, offering an alternative to the multiple wavelet hypothesis.[26] The absence of a relationship with the amount of radiofrequency energy delivered suggests that the additional role of tissue surface reduction was probably minor. Patients with persistently inducible AF after PV isolation had less prolongation of AFCL, suggesting that the PVs were less involved in the global fibrillation process or the dominance of non-PV sources or wandering atrial wavelets, possibly reflecting a more diffuse substrate supported by larger atria.

Atrial Fibrillation Cycle Length

Prior studies of AFCL in animals and humans have emphasized its role as a surrogate measure of local atrial refractoriness.[8,9,27] In contrast, the present study demonstrates changes in AFCL during ablation delivered at a remote site, providing conclusive evidence for the role of other electrophysiological variables. The AFCL was measured only within the CS, and the effect of ablation determined at other sites may have further optimized the findings. Although this site may be considered suboptimal in some patients because of its variable interconnection with the atria, it is routinely used during AF ablation and has the major advantage of being anatomically stable to allow reproducible serial measurements. In addition, recent studies have suggested that this site provides the longest cycle length with least fragmentation, allowing the unambiguous measurement of atrial activity.[28] In the present study, we observed AFCL measured within the CS to be consistent, showing low variability.

Inducibility of AF

Inducibility of AF has been the most common means to evaluate substrate modification in experimental studies,[12,29] although it has rarely been reported in clinical studies of catheter ablation.[18,30] In the present study, which included many patients with long episodes of AF and structural heart disease, AF was rendered noninducible by PV isolation in 57% and additional linear ablation prevented reinduction in 77%. Noninducibility of AF after PV isolation suggested that the substrate maintaining AF was confined within the excluded area, whereas persistent inducibility suggested persistence of perpetuating activity outside the PV regions associated with a higher risk of AF recurrence.

The reason why ablation prevents AF inducibility but leaves sustained left atrial flutter in 13% is unknown. Most flutters were macroreentrant around the PVs or perimitral, thus anatomically related to the ablated PVs serving as a central or bordering barrier.

Clinical Implications

The present study may have important clinical implications demonstrating the usefulness of AFCL as a quantitative tool for monitoring substrate changes during ablation of ongoing AF, with prolongation of AFCL indicating participation of the targeted tissue in the AF process. In this respect, the net prolongation of AFCL after mitral isthmus linear ablation raises intriguing questions about the possible role of anatomical reentry in the pathogenesis of AF in humans. In contrast, the absence of change in AFCL could mean insufficient substrate modification even if the ablation strategy may act on other variables like triggers or autonomic tone. Once sinus rhythm is restored, inducibility may be used for evaluation. Patients who are noninducible after PV isolation may not require additional substrate ablation, which is technically challenging and potentially proarrhythmic. Persistent inducibility suggests persistent substrate, higher risk of recurrence, and thus a potential need for additional drug therapy or further ablation.

Study Limitations

The parameters evaluated were collected during the course of clinical ablation procedures. Thus, we were not able to control for factors such as autonomic tone that may have influenced the AFCL. Likewise, the results of the inducibility maneuvers reflect conditions at the time of ablation that maybe susceptible to change with tissue healing and the unmasking of other sources of AF.

The usefulness of these end points for the ablation of chronic AF needs to be verified. AFCL may not be a reliable parameter in cases of significant variability of CL or when fragmented activity is dominant, as occurs in chronic AF.

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Changes in Atrial Fibrillation Cycle Length and Inducibility During Catheter Ablation and Their Relation to Outcome

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