Time to Cardioversion of Recurrent Atrial Arrhythmias After Catheter Ablation of Atrial Fibrillation and Long-Term Clinical Outcome

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Time to Cardioversion After Catheter Ablation. ***Introduction:*** **It is unclear whether early restoration of sinus rhythm in patients with persistent atrial arrhythmias after catheter ablation of atrial fibrillation (AF) facilitates reverse atrial remodeling and promotes long-term maintenance of sinus rhythm. The purpose of this study was to determine the relationship between the time to restoration of sinus rhythm after a recurrence of an atrial arrhythmia and long-term maintenance of sinus rhythm after radiofrequency catheter ablation of AF.**

Methods and Results: **Radiofrequency catheter ablation was performed in 384 consecutive patients (age 60 ± 9 years) for paroxysmal (215 patients) or persistent AF (169 patients). Transthoracic cardioversion was performed in all 93 patients (24%) who presented with a persistent atrial arrhythmia: AF (n = 74) or atrial flutter (n = 19) at a mean of 51 ± 53 days from the recurrence of atrial arrhythmia and 88 ± 72 days from the ablation procedure. At a mean of 16 ± 10 months after the ablation procedure, 25 of 93 patients (27%) who underwent cardioversion were in sinus rhythm without antiarrhythmic therapy. Among the 46 patients who underwent cardioversion at ≤30 days after the recurrence, 23 (50%) were in sinus rhythm without antiarrhythmic therapy. On multivariate analysis of clinical variables, time to cardioversion within 30 days after the onset of atrial arrhythmia was the only independent predictor of maintenance of sinus rhythm in the absence of antiarrhythmic drug therapy after a single ablation procedure (OR 22.5; 95% CI 4.87–103.88, P < 0.001).**

Conclusion: **Freedom from AF/flutter is achieved in approximately 50% of patients who undergo cardioversion within 30 days of a persistent atrial arrhythmia after catheter ablation of AF.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 1321-1325, December 2009)*

atrial fibrillation, catheter ablation, cardioversion, recurrence

Introduction

Early recurrences of atrial arrhythmias within 3 months after catheter ablation of atrial fibrillation (AF) may be transient in 30–50% of patients and may not necessarily predict long-term clinical outcome.[1,2] However, it is not clear whether early restoration of sinus rhythm by cardioversion after a recurrence is associated with an improvement in clinical outcome after catheter ablation of AF.

The purpose of this study was to determine the relationship between the time to restoration of sinus rhythm after a recurrence of an atrial arrhythmia and long-term maintenance of sinus rhythm after radiofrequency catheter ablation of AF.

The authors declare no conflicts of interest.

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Methods

Study Subjects

The subjects of this retrospective study were 93 consecutive patients who underwent transthoracic cardioversion for a persistent atrial arrhythmia. These patients were selected from a pool of 384 consecutive patients who underwent radiofrequency catheter ablation to eliminate paroxysmal (215 patients) or persistent (169 patients) AF. A persistent (>24 hours) episode of atrial flutter or AF was considered as an atrial arrhythmia in this study. The clinical characteristics of patients are shown in Table 1. Patients who have had >1 prior ablation procedures to eliminate AF were excluded from this study.

Electrophysiologic Study and Radiofrequency Catheter Ablation

All patients provided written informed consent. An electrophysiologic study was performed in the fasting state. All antiarrhythmic drugs except amiodarone were discontinued at least 4–5 half-lives before the procedure. Amiodarone was discontinued 8 weeks before the procedure. Vascular access was obtained through a femoral vein. A quadripolar catheter was placed in the coronary sinus for recording electrograms

TABLE 1

Characteristics of Patients With and Without Recurrent Atrial Arrhythmias After Cardioversion

	Total (n = 93)	No Recurrent Arrhythmias (n = 25)	Recurrent Arrhythmias (n = 68)
Ages (years)	60 ± 9	59 ± 9	60 ± 9
Male	72 (77)	20 (80)	52 (76)
Paroxysmal AF	52 (56)	10 (42)	42 (61)
Duration of AF (months)	76 ± 61	79 ± 64	75 ± 60
Ejection fraction (%)	54 ± 9	55 ± 10	54 ± 9
Left atrial size (mm)	45 ± 7	45 ± 7	45 ± 7
Coronary disease	12 (13)	2 (8)	10 (15)
Hypertension	55 (59)	15 (60)	40 (59)
Hyperlipidemia	48 (52)	13 (52)	35 (52)
Diabetes mellitus	15 (16)	6 (24)	9 (13)
Sleep apnea	14 (15)	5 (20)	9 (13)
Beta-blocker therapy	67 (72)	18 (72)	49 (72)
Calcium channel blocker therapy	28 (30)	6 (24)	22 (32)
ACE inhibitor	26 (28)	9 (36)	17 (25)
ARB	6 (7)	1 (4)	5 (7)
Digoxin	24 (26)	8 (32)	16 (23)
Statin	41 (44)	13 (52)	28 (41)
Amiodarone postablation	20 (22)	6 (24)	14 (21)
Antiarrhythmic therapy	48 (52)	12 (48)	36 (53)
Ablation of complex fractionated atrial electrograms	37 (40)	8 (32)	29 (43)
Time to recurrence after ablation (days)	37 ± 49	37 ± 53	37 ± 47
Time to cardioversion after recurrence (days)	51 ± 53	11 ± 15	66 ± 55

Data are expressed as mean ± SD. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CI = confidence interval; OR = odds ratio.

and for atrial pacing. After transseptal access, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 300–350 seconds. A decapolar ring catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) was used to map pulmonary veins (PVs). Bipolar electrograms were displayed and recorded at filter settings of 30 to 500 Hz during the procedure (EPMed Systems, West Berlin, NJ, USA).

All patients underwent antral PV isolation to isolate the PVs using an open-irrigation, 3.5-mm-tip deflectable catheter (Thermocool, Biosense Webster). If AF still persisted after antral pulmonary vein isolation (APVI), complex fractionated atrial electrograms in the left atrium and coronary sinus were targeted until AF terminated or all identifiable target sites were eliminated, at the discretion of the operator.

All patients were observed with electrocardiographic monitoring during an overnight hospital stay after the ablation. Patients were discharged home taking warfarin and low-molecular-weight heparin as a bridge to therapeutic anticoagulation.

Study Protocol

The study protocol was approved by the Institutional Review Board. All patients were seen in an outpatient clinic 3 months after the procedure and every 3–6 months thereafter. Patients were provided with an auto-triggered event monitor for 30 days, ≥3 months after the procedure. Patients were also asked to call whenever they experienced symptoms

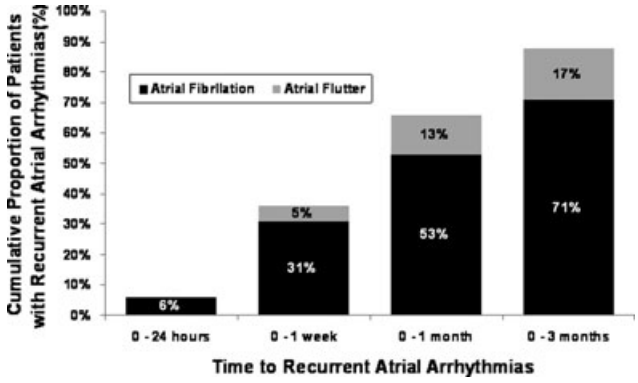

Figure 1. *Time to recurrent atrial arrhythmia after catheter ablation. Cumulative proportion of patients who developed persistent AF or atrial flutter after catheter ablation and time to recurrence (days) are shown.*

suggestive of an arrhythmia. In addition, patients were called periodically to assess their symptomatic status. Recurrent atrial arrhythmias within 3 months after the ablation were captured primarily based on the symptoms reported by the patient or evidence of an arrhythmia on an electrocardiogram. The time of recurrence of atrial arrhythmias was determined by the first occurrence of patient-reported symptoms after the ablation. In the 2 patients who were asymptomatic, the first documented episode of an atrial arrhythmia on an event monitor indicated the time of recurrence. Patients with recurrent atrial arrhythmias were treated with a class I or III antiarrhythmic drug in addition to a beta-blocker and/or calcium channel blocker for ventricular rate control. Electrical cardioversion was performed in all of the patients with persistent atrial arrhythmias. Antiarrhythmic drug therapy was discontinued within 3 months after the cardioversion in all patients who had no further episodes of atrial arrhythmias. Those patients with recurrent arrhythmias despite drug therapy were offered a repeat ablation. All asymptomatic patients were provided with a 30-day auto-triggered event monitor 3 months after the cardioversion.

Statistical Analysis

Continuous variables are expressed as mean ± 1 standard deviation and were compared using the *t*-test. Categorical variables were compared by the chi-square analysis or the Fisher exact test as appropriate. Logistic regression analysis was performed to determine the predictors of freedom from atrial arrhythmias. All analyses were performed using SPSS (15.0) for Windows (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ indicated statistical significance.

Results

Recurrence of Atrial Arrhythmias After Catheter Ablation

Among the 384 patients, 93 (24%) experienced a persistent recurrent atrial arrhythmia: AF (74 patients) or atrial flutter (19 patients), at a mean of 37 ± 49 days after the ablation procedure. There was no significant difference in the time to recurrence of AF, 36 ± 50 days, and atrial flutter, 40 ± 44 days, ($P = 0.73$). Among the 93 patients, the first recurrence occurred within 24 hours in 6%, 1 week in 37%, 1 month in 66%, and 3 months in 88% of the patients (Fig. 1).

TABLE 2

Univariate Analysis of Clinical Characteristics in Patients With and Without Recurrent Atrial Arrhythmias After Cardioversion

	OR	± 95% CI	P Value
Age (years)	0.99	0.94–1.05	0.79
Male	1.75	0.53–5.82	0.36
Paroxysmal AF	0.52	0.21–1.31	0.16
Duration of AF (months)	1.00	0.99–1.01	0.42
Ejection fraction (%)	1.02	0.96–1.07	0.57
Left atrial size (mm)	1.01	0.95–1.08	0.76
Coronary disease	1.98	0.40–9.75	0.40
Hypertension	0.95	0.37–2.43	0.92
Hyperlipidemia	0.98	0.39–2.45	0.96
Diabetes mellitus	0.48	0.15–1.53	0.22
Sleep apnea	2.34	0.28–19.69	0.43
Beta-blocker therapy	1.00	0.36–2.79	0.99
Calcium channel blocker therapy	1.53	0.30–7.77	0.61
ACE inhibitor	0.59	0.22–1.59	0.29
ARB	1.91	0.21–17.16	0.57
Digoxin	0.65	0.24–1.80	0.41
Statin	0.65	0.26–1.62	0.35
Amiodarone postablation	1.04	0.33–3.25	0.95
Antiarrhythmic therapy	0.88	0.35–2.22	0.79
Ablation of complex fractionated atrial electrograms	1.45	0.55–3.84	0.46
Time to recurrence after ablation (days)	1.00	0.99–1.01	0.98
Time to cardioversion after recurrence (days)	0.96	0.94–0.98	< 0.001

Data are expressed as mean ± SD. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CI = confidence interval; OR = odds ratio.

Time to Cardioversion

The mean time to electrical cardioversion was 88 ± 72 days after the ablation procedure. The mean interval from the first recurrence of atrial arrhythmia to cardioversion was 51 ± 53 days. Among the 93 patients, cardioversion was performed within 1 week in 34%, 1 month in 49%, and 3 months in 75%.

At the time of cardioversion, 48 of 93 patients (52%) were being treated with an antiarrhythmic drug: class IC in 20% and class III in 32% (sotalol in 10% and amiodarone in 22%). All antiarrhythmic drug therapy was discontinued within 3 months after cardioversion.

Clinical Outcome After Cardioversion

At a mean follow-up of 16 ± 10 months after a single ablation procedure and 15 ± 10 months after cardioversion, 25 of 93 patients (27%) were free of recurrent atrial arrhythmias in the absence of antiarrhythmic drug therapy. Sinus rhythm was maintained in 22 of 74 (30%) patients who underwent cardioversion for persistent AF and in 3 of 19 (16%) patients who underwent cardioversion for persistent atrial flutter (P = 0.26).

Time to Cardioversion and Clinical Outcome

The interval from atrial arrhythmia recurrence to cardioversion was shorter among patients who remained in sinus rhythm after the cardioversion, 11 ± 15 days, than patients who had recurrent atrial arrhythmias, 65 ± 55 days (P < 0.001, Table 2). Patients who underwent cardioversion within 30 days after a recurrence were more likely to remain in sinus rhythm than patients who were cardioverted after 30 days (OR 22.5, 95% CI 4.87–103.88; P < 0.001, Table 3). The proportion of patients who remained in sinus rhythm was similar whether cardioversion was performed within 1 week (16 of 32, 50%) or 1 week to 1 month (7 of 14, 50%) after the recurrence of an atrial arrhythmia (Table 3). However, only 2 of 47 patients (4%) who underwent cardioversion >1 month after the recurrence remained in sinus rhythm (P < 0.001, Fig. 2). Among all other clinical variables, there were no univariate predictors of freedom from atrial arrhythmias after cardioversion (Table 2).

Multivariate Analysis

Multivariate analysis that included age, gender, duration of AF, whether AF was paroxysmal or persistent, whether recurrent atrial arrhythmia was AF or atrial flutter, left atrial size, left ventricular ejection fraction, ablation of complex fractionated atrial electrograms, time to recurrence after ablation, time to cardioversion after recurrence of arrhythmia, and concomitant antiarrhythmic drug therapy, demonstrated that the time from atrial arrhythmia recurrence to cardioversion was the only independent predictor of maintenance of sinus rhythm in the absence of antiarrhythmic drug therapy after a single ablation procedure (P < 0.001).

Discussion

Main Findings

The main finding of this study is that after radiofrequency catheter ablation of AF, the restoration of sinus rhythm within 30 days of the onset of a persistent recurrent atrial arrhythmia is associated with a higher probability of long-term maintenance of sinus rhythm, regardless of when the arrhythmia first recurs after the ablation procedure. Freedom from recurrent atrial arrhythmias is achieved without additional catheter ablation in approximately 50% of patients who undergo early

TABLE 3

Time from Arrhythmia Recurrence to Cardioversion and Probability of Maintaining Sinus Rhythm

Time to Cardioversion After Recurrence (Days)	Total (n = 93)	No Recurrence (n = 25)	Recurrent Arrhythmias (n = 68)	OR	± 95% CI	P Value
0–7	32	16	16	22.5	4.65–108.89	<0.001
8–30	14	7	7	22.5	3.86–131.00	0.001
≥31	47	2	45	1.00	–	–

CI = confidence interval; OR = odds ratio.

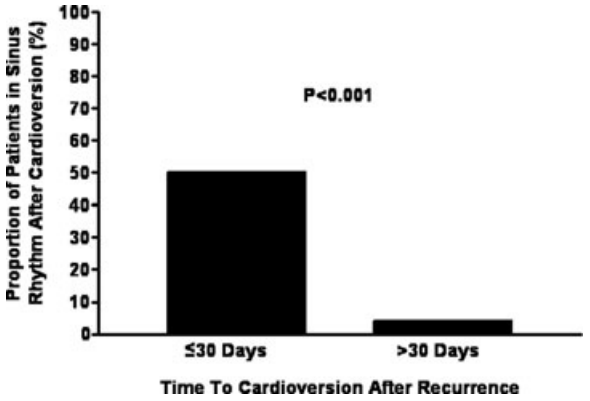

Figure 2. *Freedom from recurrent atrial arrhythmias. The proportion of patients who underwent cardioversion in ≤30 days (solid line) and >30 days (dashed line) of recurrent persistent atrial arrhythmias and who remained in sinus rhythm without antiarrhythmic drug therapy after a single ablation procedure is shown.*

cardioversion. However, if cardioversion is postponed for >30 days, virtually all patients will require a second ablation procedure.

These observations suggest that early restoration of sinus rhythm after catheter ablation may prevent progressive electroanatomical remodeling and may facilitate the long-term maintenance of sinus rhythm.

Recurrence of Atrial Arrhythmias After Catheter Ablation

As extensively reported previously, a majority of atrial arrhythmias occur within several weeks after catheter ablation of AF.[2,3] Recurrences also may occur late after ablation, however, at a much lower rate of <5–10% per year.[3,4] Although patients who experience early recurrence of AF or atrial flutter are more likely to have recurrent AF and/or atrial flutter during long-term follow-up, approximately 30–50% of patients with an early recurrence may later remain free from recurrent atrial arrhythmias.[1,2,5,6] Therefore, monitoring of the rhythm rather than routine early repeat ablation may be appropriate in these patients.

It has been suggested that early recurrences may be due to an inflammatory response or recovery of PV conduction, and that late recurrences of AF are more likely to result from emergence of new foci and mechanisms of AF in addition to recovery of conduction over previously ablated sites.[3,4,6] Therefore, it may be argued that the time of recurrence of an atrial arrhythmia after ablation rather than the time to cardioversion after the recurrence affects the probability of maintaining sinus rhythm after the cardioversion. However, the findings of this study suggest that even when adjusted for the time of recurrence, time to cardioversion is the only independent predictor of a successful long-term outcome.

Time to Cardioversion: Early Restoration of Sinus Rhythm After Catheter Ablation

Patients who underwent cardioversion within 1 month of a recurrence of an atrial arrhythmia were >20 times more likely to remain in sinus rhythm than patients who underwent cardioversion later, regardless of when the arrhythmia first recurred or whether concomitant antiarrhythmic drug therapy was utilized. The clinical outcome was similar for both AF and atrial flutter, although the 2 are mechanistically distinct arrhythmias. It may be that it is the rapid atrial rate rather than the type of atrial arrhythmia that is critical in progressive atrial remodeling.[7–9]

Early restoration of sinus rhythm is likely to prevent progressive atrial electroanatomical remodeling and facilitate long-term maintenance of sinus rhythm, consistent with the finding of the first experimental study that suggested that "AF begets AF."[8] It has been also recognized that remodeling within the PVs occurs in response to atrial tachyarrhythmias, both in experimental models and human subjects.[7,10] The probability of maintaining sinus rhythm after cardioversion in this study was independent of timing as long as cardioversion was performed within 1 month of the onset of the atrial arrhythmia. This suggests that sufficient remodeling capable of perpetuating AF develops only after 1 month of rapid atrial activation.

Pulmonary vein arrhythmogenicity may be caused by triggered activity.[11–13] It is recognized that continual stimulation of the PVs at a high frequency may maintain PV arrhythmogenicity.[14,15] Therefore, the early interruption of atrial remodeling and mechanisms capable of perpetuating AF may further inhibit PV arrhythmogenicity and facilitate long-term maintenance of AF.

Consistent with the findings of this study, a prior retrospective analysis in patients with AF demonstrated that early repeat ablation in patients who have recurrent AF after catheter ablation was associated with a higher probability of long-term maintenance of sinus rhythm, however, with a significantly higher repeat ablation rate per patient (2.5/patient).[5] It may be that if sinus rhythm was restored by early cardioversion rather than repeat ablation, half of the repeat procedures could have been avoided in that study.

Limitations

A limitation of this study is that the timing of the onset of atrial arrhythmias was based on the patient's report of symptoms or the first documented episode in asymptomatic patients. There may have been delays in the recognition of asymptomatic recurrences. However, only 2 patients in this study were completely asymptomatic during recurrent episodes of atrial arrhythmias. Due to intense clinical follow-up, any delay in recognition of an arrhythmia would not have been any longer than 1–2 months in this study.

Another limitation is that this was not a prospective, randomized study. This study provides justification for a large-scale randomized study to assess the role of early cardioversion in patients with recurrent atrial arrhythmias after catheter ablation.

Clinical Implications

The findings of this study underscore the importance of close surveillance of rhythm status after radiofrequency catheter ablation of AF. The early restoration of sinus rhythm within 1 month of the onset of an atrial arrhythmia may obviate the need for repeat ablation procedures in approximately 50% of the patients with persistent recurrent atrial arrhythmias after catheter ablation.

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