Recurrence of Atrial Fibrillation After Internal Cardioversion of Persistent Atrial Fibrillation

Prognostic Importance of Electrophysiologic Parameters

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Background  The purpose of this study was to determine whether the extent of atrial electrical remodeling affects the recurrence of atrial fibrillation (AF) after cardioversion of persistent AF (PAF).

Methods and Results  Internal atrial cardioversion was performed in 47 patients with PAF. The right atrial monophasic action potential duration (RA-MAPD) at pacing cycle lengths (PCLs) of 800–300 ms and P wave signal-averaged electrocardiogram were recorded after cardioversion. Bepridil (150–200 mg/day) and carvedilol (10 mg/day) were administered to all patients after cardioversion. Of the 47 patients, 20 had recurrent AF within 3 months. No relation was observed between age, left atrial dimension, left ventricular ejection fraction, and AF recurrence. The AF duration was significantly longer (p<0.05) and RA-MAPD at PCLs of 800 to 300 ms were significantly shorter (p<0.05) in patients with AF recurrence than in those without recurrence. The mean slope of the RA-MAPD for PCLs between 600 and 300 ms did not differ between the patients with and without AF recurrence. The filtered P-wave duration (FPD) was significantly longer in the patients with AF recurrence than in those without (p<0.05). Multivariate analysis also showed that the RA-MAPD at a PCL of 300 ms and FPD were predictors of AF recurrence (RAMAPD: p=0.038; FPD: p=0.052).

Conclusion  These results suggest that electrical remodeling related to the repolarization and depolarization may be the main contributors to early AF recurrence after cardioversion under the administration of bepridil and carvedilol. (Circ J 2005; 69: 1514–1520)

Key Words: Atrial fibrillation; Electrical remodeling; Filtered P-wave duration; Internal cardioversion; Monophasic action potential

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence increases with age. AF may cause symptoms of disability, increase the risk of thromboembolic events and is related to increased mortality. The general treatment strategy for persistent AF (PAF) is the restoration and maintenance of sinus rhythm (SR). Whether this approach is superior to anticoagulation therapy and heart rate control remains controversial, which increases the necessity to predict successful cardioversion and to maintain SR after successful cardioversion. Internal atrial cardioversion (IACV) is a useful technique for restoring SR in patients for whom external electrical cardioversion is unsuccessful or who have PAF of long duration; efficacy ranges from 70% to 90%. Once cardioversion is successful, long-term maintenance of SR is the main treatment goal. Unfortunately, despite the use of antiarrhythmic drugs and serial cardioversions, the incidence of AF recurrence ranges from 40% to 50% in the first year. It has been shown that recurrence of AF relates to atrial electrophysiologic properties. Recent animal studies have shown that AF results in a marked shortening of the atrial effective refractory period (ERP) or monophasic action potential (MAP) and loss of its physiological ability to adapt to rate. These phenomena have been implicated in the self-perpetuation of AF or its early recurrence. Furthermore, the filtered P-wave duration (FPD), as a measure of the intra-atrial conduction time, has also been shown to be related to AF recurrence. However, these data alone do not adequately clarify the relationship between atrial electrical remodeling and AF recurrence during short- and long-term follow-up (from 3 to 12 months of follow-up) in humans. Thus, we investigated the extent of atrial remodeling (atrial MAP duration (MAPD), its rate adaptation and FPD) and its relation to the recurrence of AF after cardioversion in patients with PAF.

Methods

Patients  Consecutive patients with sustained nonvalvular AF in whom the arrhythmia persisted for at least 2 months were considered for the study. The study protocol was approved by the institute’s Committee of Human Subject Research. Signed written informed consent was obtained from all study patients before they underwent an IACV and electrophysiologic evaluation performed after antiarrhythmic drug washout period of at least 5 half-lives (37 men, 10 women, mean age 59.9±11.9 years). The patients were...
Electrophysiologic Parameters of Recurrent AF

Evaluated by clinical history, physical examination, routine laboratory and thyroid function tests, and transthoracic and transesophageal echocardiography. Warfarin anticoagulation therapy was carried out in all patients to maintain a target prothrombin time between an international normalized ratio of 1.7 and 2.3 for at least 4 weeks. Patients with any of the following conditions were excluded: (1) AF from reversible causes; (2) myocardial infarction within the past 6 months or unstable angina; (3) a history of thromboembolism within the past 6 months; (4) left atrial thrombus identified by transesophageal echocardiography performed within 2 days before the cardioversion; (5) digitalis intoxication; (6) significant electrolyte imbalance; (7) implanted defibrillator or pacemaker; (8) previous treatments with bepridil, amiodarone, digoxin or calcium-channel blockers. Underlying medical conditions included hypertension (n=20), diabetes (n=3), and lone AF (n=24).

Cardioversion

IACV was performed on an elective basis. Light general anesthesia was induced with intravenous midazolam and fentanyl. R-wave synchronized biphasic shocks (3-ms/3-ms duration, HVS-02 programmable defibrillator, Ventritex, Inc, Sunnyvale, CA, USA), utilizing a right ventricular bipolar lead, were delivered via 2 identical catheters with 10 electrodes each (electrode width: 5 mm; interelectrode distance: 1 mm; Elecath, Rahway, NJ, USA) placed in the right atrial appendage and distal coronary sinus. The shock strength was increased in 50-V increments from 150 V to a maximum 600 V. The IACV was effective at 8.5±4.2 J (range 2.2–19.2 J). Successful cardioversion was defined as maintenance of SR for more than 3 h after cardioversion.

Electrophysiologic Evaluation Using the Right Atrium (RA)-MAP

Electrophysiologic evaluation was performed after 20 min of stable SR. A steerable Franz catheter (EP Technologies, Mountain View, CA, USA) was inserted through the femoral vein into the RA and MAPs were recorded from the high lateral RA. A catheter for pacing was also inserted through the femoral vein into the high lateral RA within 10 mm of the Franz catheter. The RA was paced at cycle lengths (CLs) of 800, 700, 600, 500, 400, 350, and 300 ms for 120 beats each to achieve a steady state. The RA was paced with a 2-ms pulse width at twice the diastolic threshold. The MAPD at 90% repolarization (MAPD90) was measured over 10 consecutive beats at a steady state for each CL and then averaged to obtain the mean values (Fig 1).

Electrophysiologic Evaluation Using Signal-Averaged ECG Recordings

The signal-averaged ECG was recorded 2 h after successful cardioversion and before the start of the antiarrhythmic drug treatment. The signal-averaged ECG recordings were obtained in a shielded room with the patient in the supine position by means of an MAC VU (Marquette, Milwaukee, WI, USA), a PC-based high-resolution ECG system, which includes specifically designed P wave trigger software for the analysis of the P wave. P wave signals (>200 beats) were recorded from 3 standard Frank leads (X, Y, and Z) until the noise amplitude at all points during the recording interval was reduced to <1 μV (peak noise level). The signal from each lead was filtered bidirectionally through a 40–300 Hz filter. The filtered signals for the X, Y, and Z leads were combined into a vector magnitude of the P wave.
The start and endpoint of the P wave were detected automatically and later corrected by 2 independent observers.

Follow-up

After recording the signal-averaged ECG, all patients were treated with intravenous cibenzoline (140 mg/18 h) and verapamil (20 mg/18 h). Bepridil (150–200 mg/day) and carvedilol (10 mg/day) were prescribed from the following day in all patients and continued during the follow-up period. After discharge from the hospital, patients were asked to return for an ECG recording at the first sign of AF recurrence. In addition, so that asymptomatic recurrences would not be missed, scheduled ECGs were recorded at 2 weeks, 1, 2 and 3 months, and every 3 months thereafter until AF recurred or until our follow-up procedure was completed (mean follow-up period: 12.1±14.6 months). For the purpose of this analysis, early recurrence of AF was defined as recurrence within 3 months after cardioversion because the majority of the recurrences during the 12 month follow-up occurred within 3 months according to Kaplan-Meier analysis (Fig 2).

Statistical Analysis

Data are expressed as mean±SD. The clinical parameters, MAPD90 and FPD in the patients with and without recurrence of AF were compared and analyzed by unpaired Student’s t-test. The chi-square test was used to analyze differences in nominal data. Survival curves describing the freedom from AF in all study patients were analyzed using the Kaplan-Meier method. The clinical, echocardiographic, and electrophysiologic variables were evaluated using Cox regression analysis. Statistical significance was accepted at p<0.05.

Results

SR was successfully restored in all study patients by IACV, following which 20 of 47 patients had a relapse of AF within 3 months, 24 of 45 patients had a recurrence within 6 months, and 26 of 43 patients had AF recurrence within 12 months. There were no significant differences between the patients with and without AF recurrence within 3 months with respect to clinical characteristics such as the age, sex, left atrial diameter, left ventricular ejection fraction, treatment with angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor (A-II) blockers or ß-blockers, the clinical manifestations of hypertension or congestive heart failure, brain natriuretic peptide (BNP) level, or energy required for successful IACV. The duration of AF and presence of diabetes were related to the recurrence of AF with statistical significance (Table 1); however, the number of patients with diabetes was small. With regard to the clinical characteristics, including AF duration and diabetes as noted, there were no differences between the patients with and without AF recurrence during the 6- and 12-month follow-up periods.

RA-MAPD

MAPs could not be analyzed in 5 patients because of unstable recordings. The MAP results obtained from 17 patients with AF recurrence and 25 patients without AF recurrence during the 3-month follow-up period are summarized in Table 2. The MAP90s measured at all CLs in the patients with AF recurrence were shorter than those in the patients without AF recurrence (p=0.036 for CL 800 ms, p=0.050 for CL 700 ms, p=0.035 for CL 500 ms, p=0.047 for CL 400 ms, p=0.004 for CL 300 ms, Figs 3, Table 2). The CL-dependent changes in the MAP90 (calculated as

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical Characteristics of Patients With Recurrence or Non-Recurrence of AF</th>
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<tbody>
<tr>
<td></td>
<td>Recurrence (n=20)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.7±12.7</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>17/3</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>28.7±38.5</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>42.0±5.9</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>62.8±11.4</td>
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<tr>
<td>CV energy (J)</td>
<td>8.2±4.4</td>
</tr>
<tr>
<td>FPD (ms)</td>
<td>159.4±51.2</td>
</tr>
<tr>
<td>MAPD90/CL300 (ms)</td>
<td>168.1±17.7</td>
</tr>
<tr>
<td>ACEI or A-II blocker (+/-)</td>
<td>7/13</td>
</tr>
<tr>
<td>ß-blocker (+/-)</td>
<td>5/15</td>
</tr>
<tr>
<td>HT (+/-)</td>
<td>9/11</td>
</tr>
<tr>
<td>Diabetic (+/-)</td>
<td>3/17</td>
</tr>
<tr>
<td>CHF (+/-)</td>
<td>3/17</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>143.1±132.0</td>
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</tbody>
</table>

MAPD90, atrial monophasic action potential duration at 90% repolarization; CV, cardioversion; FPD, filtered P wave duration; MAPD90/CL300, monophasic action potential duration at a cycle length of 300 ms; ACEI, angiotensin-converting enzyme inhibitor; A-II, angiotensin II receptor; HT, hypertension; CHF, congestive heart failure; BNP, brain natriuretic peptide.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>MAPD90 and Rate-Adaptation in Patients With Recurrence or Non-Recurrence of AF at All Constant Pacing CLs</th>
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<tbody>
<tr>
<td></td>
<td>Recurrence Non-recurrence p value (n=20) (n=27)</td>
</tr>
<tr>
<td>CL (ms)</td>
<td>Slope values between CLs of 600 and 300 ms</td>
</tr>
<tr>
<td>300</td>
<td>350</td>
</tr>
<tr>
<td>168.1±17.7</td>
<td>177.5±17.6</td>
</tr>
<tr>
<td>189.8±25.7</td>
<td>190.6±23.4</td>
</tr>
<tr>
<td>p value</td>
<td>0.004</td>
</tr>
</tbody>
</table>

MAPD90, atrial monophasic action potential duration at 90% repolarization; AF, atrial fibrillation; CLs, cycle lengths.
the slope of the line in which the MAPD90 was plotted against CLs between 600 and 300 ms) in the patients with AF recurrence did not differ significantly from those of the patients without AF recurrence (Table 2). The MAPD90s measured at all CLs and the CL-dependent changes in the MAPD90 in the patients with and without AF recurrences exhibited the same results at 6- and 12-months of follow-up as those obtained at 3-months (6 month MAPD90s: p<0.05 for CL 800~300 ms, slope values: NS; 12 month MAPD90: p<0.05 for CL 800~300 ms, slope values: NS).

**FPD**

The FPD could not be measured in 3 patients with SR because the endpoint of the P wave extended into the QRS complex. The FPD was significantly longer in the patients with AF recurrence than in those without AF recurrence at (less than) 3 months (159.4±10.2 vs 149.7±16.1 ms, p<0.05, Table 1). The FPD was also found to be significantly longer in the patients with AF recurrence than in those without less than 6 and 12 months of follow-up (6 months: 159.6±9.7 vs 149.2±16.7 ms, p<0.05; 12 months: 159.9±10.0 vs 149.2±17.0 ms, p<0.05).

**Multivariate Predictors of the Recurrence of AF**

Multivariate Cox regression analysis with AF recurrence as the response variable and other clinical, echocardiographic, and electrophysiologic variables showed that a shorter MAPD90/300 was associated with AF recurrence (hazard ratio 1.020, 95% confidence interval (CI) 1.001–1.041, p=0.038, Table 3). The FPD and AF duration were not found to be significant independent predictors of AF recurrence, but the FPD had a weak correlation to AF recurrence.
The present study evaluated the electrophysiologic predictors of AF recurrence after performing IACV in patients with PAF. During a 3-month follow-up period, the MAPD90 in the patients with AF recurrence was shorter than that in the patients without AF recurrence, but the CL-dependent changes in the MAPD90 did not differ between the 2 groups. The FPD was also significantly longer in the patients with AF recurrence than in those without. These electrophysiologic parameters (MAPD90 and FPD) exhibited similar tendencies between the patients with and without AF recurrence during both the 6- and 12-month follow-up periods.

**Clinical and Echocardiographic Variables Following Cardioversion of PAF**

The clinical variables that have been reported to be associated with AF recurrence include age, AF duration, type of underlying heart disease, functional class, and size of the left atrium. Differences in patient selection criteria, types of antiarrhythmic agents given before and after cardioversion, duration of follow-up, and the retrospective nature of some of these studies might explain the discrepancies in the clinical variables identified. In the present study, we found a significant relationship between AF duration and AF recurrence (p<0.05), but the AF duration was not related to AF recurrence in the multivariate analysis, which suggests that other factors predict AF recurrence more significantly than AF duration.

**RA-MAPD Following Cardioversion of PAF**

Several previous studies in animal and human models have shown that sustained rapid atrial rates, such as those that occur in AF, result in significant shortening of refractoriness or repolarization (ERP/MAP) and the ability of ERP/MAP to adapt to rate. The progressive shortening of the ERP and loss of its ability to adapt to rate because of sustained AF has also been shown in animal and human studies suggesting that a shortening of the ERP/MAP and abnormal rate adaptation may be correlated with AF recurrence. In fact, several recent studies have also shown that a short atrial ERP/MAP is an independent predictor of AF recurrence. In the present study, the patients with recurrence of AF had a shorter RA-MAPD90, as compared with those without, and the shorter MAPD90/CL was a powerful predictor of AF recurrence in the multivariate analysis. The shorter ERP/MAP in the relapsed patients was a consistent finding, but abnormal rate adaptation remains controversial. Biffi et al showed that an abnormal relationship of the atrial ERP to CL was the most powerful predictor of AF recurrence (odds ratio 31, 95% CI 3.7–266). In contrast to their finding, our study showed that the CL-dependent changes in the RA-MAPD90 did not differ between the patients with and without AF recurrence. Furthermore, although our study showed that it was not possible to compare the AF patients with control patients without AF, the RA-MAPD90 adaptation to the rate in both the patients with and without AF recurrence was found to be nearly normal (slope values >0.07, Table 2) using the definition shown in the report of Pandorzi et al. This discrepancy in the rate adaptation of atrial refractoriness may contribute not only to the use of a different refractoriness parameter (MAP or ERP), patient selection, patient number, or clinical setting, but also to some factors that may affect the MAP/ERP directly. An interesting report by Shinagawa et al showed that in dogs with congestive heart failure, atrial tachycardia reduced the ERP to a lesser extent than it did in dogs without congestive heart failure, did not alter the ERP rate adaptation, and reduced the conduction velocity. The AF patients in our study had subclinical heart failure because of the increased plasma BNP concentration (143.1±132.0 pg/ml) despite normal ventricular ejection fraction (62.8±11.4%), suggesting that this factor might affect the RA-MAPD90 adaptation to rate.

**Signal-Averaged P-Wave Duration Following Cardioversion of PAF**

The signal-averaged P wave can detect atrial conduction disturbances more precisely than the 12-lead ECG P-wave. Previous studies in both animals and humans showed that electrical remodeling by AF increases the intra-atrial conduction time. Opolski et al demonstrated that the FPD was longer in patients with recurrence of AF within 6 months than in those without recurrence (145±12 vs 130±11 ms, p<0.001). In contrast, Stafford et al showed no difference in the FPD between those patients who had AF recurrence within 4 weeks of cardioversion and those who did not (156±2 vs 151±4 ms, p=NS). The discrepant results between the studies may have been caused by the selection of patients at high risk for recurrence without a low-risk group for comparison (only 3 of 75 cardioversions remained in SR in more than 3 months). Our study revealed that the FPD was significantly longer in the patients with AF recurrence than in those without, and this significance remained in the multivariate Cox regression analysis. The data obtained in the previous studies together with our data indicate that the use of the FPD for predicting AF recurrence is still controversial. However, considering the discrepancy in the FPD for factors such as patient selection, different signal-averaging methods used, and use of antiarrhythmic drugs, the FPD may be a noninvasive simple method for predicting AF recurrence after cardioversion.

**Relationship of the RA-MAPD and Signal-Averaged P-Wave Duration to AF Recurrence During the 3, 6 and 12-Month Follow-up Periods**

The MAPD90s measured at all CLs, CL-dependent changes in the MAPD90 and FPD also had similar results between the patients with and without AF recurrence within not only 3 months but also within 6 and 12 months of follow-up. Furthermore, using multivariate analysis, the MAPD90/CL was the only variable that significantly correlated with AF recurrence (p=0.038), and the correlation between the FPD and AF recurrence was weak (p=0.052). These findings may support the observation that the predictors of early AF recurrence (within 3 months) might remain crucial for AF recurrence within even 6 and 12 months of follow-up because the majority of patients with AF recurrence (20 of 26 relapsed patients: 77%) had early recurrence within 3 months during our 12-month follow-up (Fig 2). Thus, this may imply that the electrical remodeling of refractoriness (MAP/ERP) and depolarization (FPD) is reversible within 3 months after conversion to SR, and that most AF patients in whom these reversible electrical changes occur within 3 months will maintain SR for 12 months. In fact, reversal of the refractoriness or repolarization change occurred within several days and moreover, depolarization...
tion changes, as measured by the P wave or FPD, were reversible within several weeks or months.

Maintenance of SR by Bepridil and Carvedilol

Amiodarone has been shown to be more effective than other antiarrhythmic agents in preventing AF recurrence. However, we used bepridil and carvedilol for the maintenance of SR after cardioversion. Recent reports have shown that bepridil does not have the adverse effects of amiodarone and has a high rate of conversion of AF to SR. Furthermore, because bepridil has the electrophysiologic characteristics of class Ib, III, and IV drugs and carvedilol has the electrophysiologic characteristics of class II drugs,47,48 we expected their combined use to have electrophysiologic effects similar to those of amiodarone, except for the effects on the thyroid hormone. We expected the major electrophysiologic effect of bepridil to be prolongation of the atrial ERP or MAPD because AF recurrence correlated with MAPD90 shortening according to our present results.

Fujiki et al.49 and Nakazato et al.40 reported that 83% (18 of 22 patients) and 81% (70 of 86 patients) of PAF patients were free of AF recurrence at 12-months and 18-months of follow-up, respectively. In contrast to those studies, the rate of maintaining SR at 12 months of follow-up using the combination of bepridil and carverilol in the present study was lower (21 of 47 patients: 44.7%, Fig 2). The high recurrence rate may have been related to the patient selection, or the use and dose of the antiarrhythmic drugs. The mean AF duration in our subjects was longer (19.3±28.1 months) than that in the reports by Fujiki et al. (17.8 months) and Nakazato et al. (5.2 months) and also, we started these drugs after cardioversion.

Study Limitations

Our data on the MAPD are limited to the RA, and the left atrium was not included in our study. The AF-induced changes in the action potential configuration from one site may not be applicable to other parts of the atrium, and animal experiments have shown regional heterogeneity of the atrial APD resulting from differences in the ionic currents involved in repolarization.

Furthermore, regional differences in the recovery of the tachycardia-induced changes in the atrial electrophysiological properties have been shown in animals.

A second limitation is that the FPD that predicted AF recurrence might have been applicable only to the specific device (MAC VU) that we used. Third, following the cardioversion, all patients in our study were treated with antiarrhythmic drugs (bepridil and carvedilol), which might have affected the AF recurrence rate. Finally, clinical studies have shown that ACEI reduce the incidence of AF. We, however, found no correlation between the use of ACEI, A-II blockers or β-blockers used before cardioversion and AF recurrence. Thus, further studies are needed to confirm the relationship between pretreatment with drugs that prevent electrical or structural remodeling and AF recurrence.

Conclusions

This study, which sought to identify the relationship between the recurrence of AF and clinical and electrophysiologic parameters, showed that patients with AF recurrence had a significantly shortened RA-MAPD and prolonged FPD. Thus, electrical remodeling of both atrial repolarization and depolarization contains prognostic information for the recurrence of AF after successful cardioversion.
42. Nobe S, Aomine M, Arita M. Bepridil prolongs the action potential duration of guinea pig ventricular muscle only at rapid rates of stimulation. Gen Pharmacol 1993; 24: 1187 – 1196.