Atrial premature complexes and heart rate have prognostic significance in 1-month atrial fibrillation recurrence after electrical cardioversion

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Aims The aim of this study was to investigate the significance of simple 24-h Holter (24H) data after electrical cardioversion (CV) for atrial fibrillation (AF) recurrence.

Methods We prospectively studied 47 consecutive patients subjected to CV, who successfully converted to sinus rhythm. All underwent echocardiography and 24H after CV. AF recurrence was studied at 14 days and 1 month by second 24H or by interim report of AF.

Results About 53.2% remained in sinus rhythm (group I) and the rest recurred to AF (group II). Group I had fewer atrial premature complexes per hour (APC/h) ($P = 0.002$) and lower maximum (max HR), average, and minimum heart rates compared with group II (all $Ps < 0.05$). The optimal value of APC/h and max HR with best sensitivity and specificity was 32 APC/h and 90 bpm, respectively. These findings were the predictors of AF recurrence [hazard ratio (HR) = 4.5 with 95% CI = 1.7–11.7 and HR = 4.3 with 95% CI = 1.7–10.9, respectively]. Patients with the combination of both predictors had greater HR of AF recurrence compared with those with <32 APC/h and max HR <90 bpm (HR = 8.8 with 95% CI = 2.5–31.4).

Conclusion Patients with frequent APC/h and high max HR are at high risk for 1-month AF recurrence after electrical CV.

KEYWORDS
Atrial fibrillation; Cardiomyopathy; Atrial premature complexes; Heart rate

Introduction

Atrial fibrillation (AF) is a common arrhythmia and its incidence is increasing with age and the presence of structural heart disease. AF is frequently associated with several cardiac diseases.

Direct current cardioversion (CV) is a widely used and effective method to restore sinus rhythm in AF patients. The immediate success rate of electrical CV varies from 67 to 94%. However, the recurrence rate is high, ~14–50% at one-year follow-up, and it is greater mainly in the first month after electrical CV. Factors that predispose to AF recurrence are gender, age, AF duration before CV, number of previous recurrences, left atrial size or function, and the presence of coronary heart disease or pulmonary or mitral valve disease. Left atrial size, patient’s age, and etiology of AF have become less predictable factors of AF recurrence with the use of amiodarone.

In a previous prospective study of our group, we had investigated the role of atrial premature complexes (APCs) and/or the presence of supraventricular tachycardia (SVT) recorded early after electrical CV as prognostic factors for one-year AF recurrence.

Furthermore, in a recent paper, researchers have identified that a triggering APC, detectable with ambulatory Holter recording, was the onset mechanism of paroxysmal AF in 95% of patients.

In this study, we further investigated the prognostic significance of atrial arrhythmias and/or the maximum (max HR), average (avr HR), and minimum heart rate (min HR) of a 24-h Holter (24H) recording immediately after electrical CV at 1-month follow-up. We decided to choose a follow-up of 1 month, because of the fact that the rate of 1-month AF recurrence after electrical CV remains high. The identification of predisposing factors for AF recurrence (high- or low-risk patients) may affect the potential changes of anti-arrhythmic medications or may also have consequences for choosing non-pharmacological treatment, for instance catheter-ABLation, resulting in a greater possibility of sinus rhythm maintenance.

Methods

Patient population and study design

In our study, we prospectively studied 47 consecutive patients who underwent electrical CV at the Onassis Cardiac Surgery Center for AF and who were successfully converted to sinus rhythm. All
patients continued the same antiarrhythmic medication and other drugs before, during, and after the CV. The majority (45 patients) had an initial attempt of pharmacological CV.

The antiarrhythmics used were amiodarone (loading dose: 600–1200 mg daily for 7–10 days and maintenance dose: 1000–1400 mg per week), propafenone (450–900 mg daily), or sotalol (120–240 mg daily). The dosage of propafenone and sotalol maintained as above for at least 3 days before CV. The dosage of amiodarone remained the same for at least 3 weeks before CV. All treatment modalities had been at the discretion of their referring physicians.

All patients received antiocoagulation (per os acenocoumarol or warfarin) with a target INR 2–3 for 3 weeks before and 4 weeks after CV.

Patients were excluded from the study if (i) the cause of AF was recent (<6 months) open heart surgery or if the patient who had undergone electrical CV had open heart surgery during the follow-up; (ii) the paroxysm of AF was due to a reversible cause, such as thyrotoxicosis, excessive alcohol consumption, or it had occurred during acute myocardial infarction or infection; and (iii) a permanent pacemaker was present.

All patients underwent a clinical and echocardiographic study before CV. We examined the left ventricular function (measurement of fractional shortening), left atrial size (measurement of left atrial appendage, since embolic events may be standardly noted even with adequate anticoagulation).

During electrical CV, we used sedation. Shocks were biphasic and we used anteroposterior electrode positions, with an initial dose of 200 J; if this shock was unsuccessful, a 300-J shock was performed. Immediately after successful CV, a 24 h recording was instituted. All of the patients had at least 18-h Holter recordings. Automatic analysis was initially performed. At least three consecutive APCs at a rate >120 per min were recorded as a run of SVT. Two experienced cardiologists corrected the automatic analysis of the Holter recording. The number of APCs, which was calculated, included both isolated APCs as well as those occurring in the runs of SVT. We recorded the following Holter findings: mean number of APCs per hour for the entire duration of Holter recording (APC/h), APCs per hour of the first 6 h of the recording (APC/h 0–6), APCs per hour of the second 6 h of the recording (APC/h 6–12), runs of SVT, and max HR, min HR, and avr HR.

The prospective follow-up of the patients included physical examination, electrocardiography at 15 days, and a Holter 1 month after CV. The Holter recordings were performed in order to identify the asymptomatic recurrences of AF. In addition to this, we advised every patient of our study that whenever he/she had symptoms, such as palpitations, or whatever that would have suggested an AF recurrence to come for an urgent visit in order to perform an ECG and detect any possible recurrence of the arrhythmia.

The study complies with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol, and an informed consent of the subjects has been obtained.

### Statistical analysis

We used t-test for independent samples to compare the means of continuous variables and χ² test for qualitative variables. We used the Kolmogorov–Smirnov test for normality in order to evaluate the assumption of t-test. In order to take normal distributions for the variables APC/h, APC/h 0–6, and APC/h 6–12, the natural logarithm of the above variables was used. Cut-off analysis revealed the level of APC/h and max HR with best combination of sensitivity and specificity that discriminate the patients according to whether they had an AF recurrence or not.

Discriminant analysis after calculating λ-Wilk’s showed which of the continuous variables had the strongest discriminating ability for the outcome. We used linear regression in order to identify the linear correlations between continuous variables using R². A Cox-proportional hazard model was used to assess the association of baseline variables with the endpoint of AF recurrence. Survival curves were calculated using the Kaplan–Meier method. Log-rank test was used to test the null hypothesis that the survival functions were equal for the two compared groups, based on the aforementioned cut-off values of APC/h and max HR.

Categorical data were summarized as frequencies or percentages. Continuous data were summarized as mean ± standard deviation (SD). Significance was set at the 0.05 level for all the analyses. STATA 8.0 (STATA corp., College Station, TX, USA) software was used.

### Results

During 1 month of follow-up, 25 patients (53.2 %) remained in sinus rhythm (group I), whereas in 22 patients (46.8 %) AF recurred (group II). Age, sex, underlying disease, left atrial size, fractional shortening, duration of AF, and the medication taken were similar between the two groups (all P values = NS, Table 1).

To identify the factors with prognostic significance for AF relapse, we compared the means of the natural logarithm of the following variables: ln APC/h, ln APC/h 0–6, and ln APC/h 6–12 between the two groups. Group II had significantly higher ln APC/h compared with group I (4.07 ± 1.29 vs. 2.85 ± 1.25, P = 0.002). The means of ln APC/h 0–6 and ln APC/h 6–12 of group II were significantly higher at various levels of significance (5.66 ± 1.19 vs. 4.80 ± 1.64).

### Table 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (years)</td>
<td>63.3 ± 9</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>13:12</td>
<td>11:11</td>
</tr>
<tr>
<td>Fractional shortening ± SD</td>
<td>31.3 ± 6.5</td>
<td>30.7 ± 5.4</td>
</tr>
<tr>
<td>LA size ± SD (mm)</td>
<td>48.5 ± 6.3</td>
<td>50 ± 8.3</td>
</tr>
<tr>
<td>AF duration (weeks)</td>
<td>14.9 ± 13.8</td>
<td>15.2 ± 14</td>
</tr>
<tr>
<td>Underlying disease n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>8 (32)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Valvular</td>
<td>8 (32)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Hypertention</td>
<td>8 (32)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 (4)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4 (16)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Beta-blockers n (%)</td>
<td>12 (48)</td>
<td>8 (36.3)</td>
</tr>
<tr>
<td>Antiarrhythmic medication n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>12 (48)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>5 (20)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (12)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>4 (16)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>None</td>
<td>1 (4)</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

All P values were non-significant.

Patients were analysed as receiving amiodarone vs. any other antiarrhythmic treatment.

LA, left atrium; AF, atrial fibrillation; CHD, coronary heart disease.
and 5.9 ± 1.47 vs. 4.79 ± 1.68, respectively, both \( P \) values < 0.05). Cut-off analysis showed that the optimal value of APC/h with best sensitivity and specificity was 32 APC/h (sensitivity = 73%, specificity = 72%). We compared the levels of the other variables max HR, Min HR, and Avr HR between the two groups. We found that the patients with AF recurrence had higher means of max HR, min HR, and avr HR [99 ± 19 vs. 82 ± 14, 52 ± 7 vs. 47 ± 6, and 68 ± 10 vs. 61 ± 8, respectively, at various levels of statistical significance (all \( P \) values < 0.05)]. Cut-off analysis showed that the value of max HR with best sensitivity and specificity was 90 bpm (sensitivity = 73%, specificity = 76%).

Discriminant analysis showed that max HR was the strongest discriminator for AF recurrence (\( \lambda \text{-Wilk's}_1 = 0.804 \)) followed by avr HR (\( \lambda \text{-Wilk's}_2 = 0.882 \)), minimum HR (\( \lambda \text{-Wilk's}_3 = 0.905 \)), and APC/h (\( \lambda \text{-Wilk's}_4 = 0.905 \)) (data not shown in texts or tables).

We used simple linear regression of max HR (as dependent variable) and total APC/h (as independent variable) and we found that max HR and total APC/h had no linear correlation between them. In other words, APC/h interpreted only 5.4% of the total variance of max HR \( R^2 = 0.054 \), \( P = 0.16 \).

The occurrence and the number of SVT of any duration were non-predictive (both \( P \) values = NS).

Cox regression models showed that the aforementioned prognostic factors (>32 APC/h and max HR >90 bpm) were strong predictors of AF recurrence during the short-term follow-up [hazard ratio (HR) = 4.5 with 95% CI = 1.7–11.7 and HR = 4.3 with 95% CI = 1.7–10.9, respectively). Patients with the combination of both predictors had greater HR of AF recurrence compared with those with <32 APC/h and max HR <90 bpm (HR = 8.8 with 95% CI = 2.5–31.4).

Figure 1 is a graph of a Kaplan–Meier survival estimate, which represents the probability of not having an AF recurrence during the 1-month of follow-up. Log-rank test revealed that there was a difference between the AF recurrence experience of patients with >32 APC/h and those without this finding (\( P < 0.001 \)) (Figure 2).

Similarly, there was a difference between the AF recurrence experience of patients with max HR >90 bpm and those without this predictor (\( P < 0.001 \)) (Figure 3).

Furthermore, we compared the survivor function of patients with max HR >90 bpm and <32 APC/h with the survivor function of those having max HR <90 bpm and <32 APC/h. Patients having only one of the above predictors (i.e. either max HR >90 bpm or >32 APC/h) were excluded from the analysis. Subsequently, we ended in a significant difference in favour of the group without the combination of the aforementioned predictors (\( P < 0.001 \)) (Figure 4).

**Discussion**

In our study, we collected data from a 24H recording after successful CV and we tried to find the potential prognostic factors that influence the maintenance of sinus rhythm during 1 month of follow-up.

**Significance of atrial arrhythmias**

We found that >32 APC/h were highly predictive for 1-month AF recurrence. This finding had moderately good sensitivity and specificity. In our previous-mentioned study, we found that >10 APC/h in the Holter recording after CV was a significant factor for the recurrence of arrhythmia during 1-year follow-up with 70.3% sensitivity and 76.5%

![Figure 1](https://i.imgur.com/3Q5Q5Q.png)

**Figure 1** A Kaplan–Meier survival estimate, which represents the probability of not having an AF recurrence during the 1 month of follow-up. Time 0 is the day of cardioversion.

![Figure 2](https://i.imgur.com/5Q5Q5Q.png)

**Figure 2** Kaplan–Meier curves for the two levels of APC/h for patients with >32 APC/h and those with <32 APC/h. Time 0 is the day of cardioversion.

![Figure 3](https://i.imgur.com/5Q5Q5Q.png)

**Figure 3** Kaplan–Meier curves for the two levels of max HR for patients with max HR >90 bpm and those with <90 bpm. Time 0 is the day of cardioversion.
disagreement. In the study of Chong et al.,24 the patient cohort was older, the follow-up was longer (6 months), and many patients had antiarrhythmic medications changed during the aforementioned follow-up.

**Significance of heart rate**

Another finding that predicted the maintenance of sinus rhythm was the level of max HR, avr HR, and min HR. Specifically, we found that patients without 1-month AF recurrence had a lower heart rate in general. In other studies, researchers found that increased heart rate variability (HRV) was associated with late AF recurrence after electrical CV of persistent AF.25 In addition to this, spectral analysis of HRV revealed that greater low/high frequency ratio was associated with AF recurrence after electrical CV, which implies that increased sympathetic and reduced vagal modulation of sinus rhythm characterized the patients with an early AF recurrence.26 Obviously, any measurement of any level of heart rate is an easy way of identifying high-risk patients for AF recurrence, which can be obtained not only by a Holter recording, but also by following the patient with a simple monitor. Probably, a medication that reduces the adrenergic overactivity, which may predispose to AF ‘sympathetic’ etiology as opposed to ‘vagal’, in order to make the APC/h fewer could be a logical approach. This would especially hold true in the patients in whom an attempt at heart rate control was not well tolerated. A previous study has proved that beta-blockers prevent subacute recurrences of persistent AF in hypertensive patients.27 Recently, Blich and Edout found that in patients with persistent and chronic AF treatment with beta-blockers prior to CV was an independent factor predicting long-term success. However, Raitt et al.22 reported different data, i.e. a slower heart rate to be predictive of AF recurrence, but only at 10-min and 1-h recording after CV. But this finding is a different entity based on only 1-h duration compared with the 24H recording of our study.

**Significance of other factors**

Concerning other factors, such as age, gender, underlying disease, left atrial size, left ventricular fractional shortening, duration of AF, and the medication taken, no differences between the two groups were found. The small number of patients may be responsible for this result. On the other hand, the homogeneity of the groups gives us some certainty that the above factors did not have any real influence on AF recurrence. However, it would be of great interest to perform subgroup analyses as far as the total number of APC/h is concerned according to the underlying disease of the baseline characteristics of patients. But this was impossible to do, because of the fact that the study enrolled a small number of patients and there was no statistical power enough to establish a difference that really exists.

**Limitations**

A combination of frequent (> 32) APC/h and max HR > 90 bpm was associated with high risk of AF recurrence as already stated. It could be postulated that frequent APC/h contribute to a greater level of heart rate through higher adrenergic activity in the patients not receiving sotalol. However, linear regression of max HR and total APC/h revealed that APC/h interpreted only 5.4% of the total variance of HR. This means that APC/h contributed very little to the level of max HR.

We cannot definitely exclude that between the scheduled follow-up visits, some of the patients had asymptomatic recurrences of AF, which spontaneously converted to sinus rhythm. However, many attempts of pharmacological CV before electrical CV were unsuccessful, and it would be improbable that many AF recurrences and spontaneous conversions to sinus rhythm occurred at 1 month, to be of clinical importance. In addition to this, all of the patients had been advised to report whatever could be suggestive of AF recurrence, and the second Holter recording at 1 month of follow-up helped us to diagnose these probable asymptomatic recurrences.

**Conclusions**

We have identified two factors (APC/h and heart rate) derived from a 24H recording immediately after electrical CV, which are highly predictive of 1-month AF recurrence. These findings may prompt drug therapy changes to prevent recurrence. Alternatively, frequent APCs could also stimulate physicians to refer patients for catheter ablation, given that the myocardium surrounding the
pulmonary veins may be an important source of ectopic beats triggering AF.

Conflict of interest: none declared.

References