Factors Predicting Success Rate and Recurrence of Atrial Fibrillation after First Electrical Cardioversion in Patients with Persistent Atrial Fibrillation

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Summary

Background: The recurrence rate of atrial fibrillation (AF) after elective cardioversion is high.

Hypothesis: The study aimed to identify clinical predictors for successful electrical cardioversion and maintenance of sinus rhythm after a first electrical cardioversion in patients with persistent AF without concomitant antiarrhythmic drugs of class I and III.

Methods: Consecutive outpatients ($n = 166$) with persistent AF for > 1 month, scheduled for elective cardioversion, were prospectively included in the study. A clinical investigation, echocardiographic assay, and Holter electrocardiogram (ECG) before and ECG 4 weeks after cardioversion, were performed in all patients.

Results: The mean age of the patients was 68 years (range 45–83) and duration of AF was 5 (1–48) months. Sinus rhythm was established in 124 (75%) patients. In multivariate analysis, only duration of AF < 6 months ($p < 0.04$, odds ratio [OR] 2.2, 95% confidence interval [CI] 1.1 to 4.7) and patients weight ($p < 0.03$, OR 2.3, 95% CI 1.1 to 4.8 for weight < 80 kg) were identified as independent predictors of successful cardioversion. At 4 weeks after cardioversion, only 46 (37%) of 124 patients maintained sinus rhythm. Independent factors for maintenance of sinus rhythm, in multivariate analysis, were AF < 3 months ($p < 0.04$, OR 2.5, 95% CI 1.1 to 5.6), treatment with beta blockers ($p < 0.00001$, OR 7.0, 95% CI

3.0 to 16.3) or verapamil/diltiazem ($p < 0.04$, OR 3.6, 95% CI 1.1 to 12.1), and right atrial dimension < 37 mm ($p < 0.02$, OR 5.9, 95% CI 1.4 to 25.4).

Conclusions: In patients with persistent AF, the patient's weight and the duration of AF are independent predictors for a successful cardioversion. Short duration of AF, treatment with beta blockers or verapamil/diltiazem, and right atrial area/dimension are independent predictors for maintenance of sinus rhythm.

Key words: atrial fibrillation, cardioversion, arrhythmias

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence increases with age.¹ Atrial fibrillation may cause disabling symptoms and risk of thromboembolic events, and it is related to increased mortality.^{2,3} Therefore, the general treatment strategy of persistent AF is restoration and maintenance of sinus rhythm. Whether this approach is superior to anticoagulation therapy and heart rate control remains unclear.⁴ This increases the necessity to predict cardioversion success rate and maintenance of sinus rhythm after successful cardioversion. External electrical cardioversion remains the technique of choice in patients with persistent AF, with a success rate ranging from 65 to 90%.^{5–7} Several studies have evaluated factors that predict success rate and maintenance of sinus rhythm after cardioversion in patients with AF.^{6–15}

The duration of AF has most consistently been found to correlate with the likelihood of impaired success rate and recurrence of AF. The age of patients also seems to be an important factor, even though contradictory results have been reported.^{8,9,15} Other factors, the presence of underlying structural heart disease, functional New York Heart Association (NYHA) class, mitral valve disease, or left ventricular enlargement all show inconsistent results. The left atrial diameter seems to increase with duration of AF.^{16,17} The fact that atrial size fails to reach significance in many studies may reflect its dependence on duration of AF. Moreover, cardiac di-

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mensions measured with echocardiography are rarely corrected for body surface area (BSA). It is therefore unknown whether the heart volume per se or the relative dilatation of the heart chambers influences success rate and recurrence of AF. In patients with uncertain duration of AF, disposal of objective parameters are important.

The role of the autonomic nervous system in the initiation of AF has been emphasized.¹⁸ The value of estimation of heart rate and rate variability before cardioversion in patients with chronic AF has not been evaluated.^{19,20} Recent data indicate that slow ventricular rate predicts outcome of cardioversion and relapse of AF.²¹

The present study was designed to evaluate the effect of clinical, echocardiographic, and heart rate variability variables on success rate and maintenance of sinus rhythm after a first electrical cardioversion in patients with persistent AF of a duration of > 1 month.

Methods

Patients

In all, 166 consecutive outpatients were included from two centers in Stockholm—South Hospital and Karolinska Hospital. Inclusion criteria were a clinical diagnosis of persistent AF for at least 1 month, verified with 24-h electrocardiogram (ECG), and indication for elective electric cardioversion. Patients with atrial flutter for longer than 6 of 24 h during Holter monitoring were excluded. Other exclusion criteria included previous electric or pharmacologic cardioversion, hyperthyroidism, serum potassium < 3.7 mmol/L, and myocardial infarction or cardiac surgery within the last 2 months. No antiarrhythmic drug treatment known to influence success rate or maintenance of sinus rhythm (e.g., Vaughan Williams class I and III, including sotalol) were allowed. Treatment with digoxin, diltiazem, verapamil, or beta blockers for ventricular rate control was allowed. All patients were treated with warfarin, International Normalized Ratio (INR) of 2.0 to 3.0, for at least 3 weeks before and 4 weeks after cardioversion. A careful history, examination of the patient's records, and a review of available ECGs was performed in all patients in an attempt to determine the duration of AF.

Cardioversion

Electric cardioversion was performed on an elective basis according to clinical practice at each hospital. Light general anesthesia was induced by intravenous propofol. Paddles were placed in the right second intercostal space and in left-sided lateral position along the midaxillary line. Delivery of shocks was started with 100 or 200 J, and thereafter, if unsuccessful, with stepwise increase with at least one attempt at 360 J. Successful cardioversion was defined as the maintenance of sinus rhythm for > 1 h after cardioversion. All patients underwent a clinical follow-up, including a 12-lead ECG, 4 weeks after cardioversion.

Echocardiographic Measurements

Two-dimensional transthoracic echocardiography was performed in all patients before cardioversion. Left and right atrial area were determined from the four-chamber apical view²² and calculated from the formula $(0.5 \times \text{medial-lateral diameter}) \times (0.5 \times \text{inferior-superior diameter}) \times \pi$.¹⁷ All dimensions were also corrected for BSA.²³ There is no consensus regarding the choice of optimal method for estimation of left ventricular function with echocardiography in AF.²⁴ The ejection fraction (EF) is influenced by irregular RR intervals and rapid heart rate. In an attempt to achieve a value of EF representative for left ventricular systolic function independently of AF, we did not measure consecutive heart beats. Instead, the investigator chose a minimum of five heart beats that were judged to be the most representative for left ventricular systolic function. Two different methods were used: visual EF and wall motion score index (WMSI).²⁵ For calculation of WMSI, the left ventricle was divided into 16 segments as proposed by the American Society of Echocardiography.²⁶ A minimum of 12 measurable segments in each patient were required for acceptance. Valvular stenosis or regurgitation was defined as presence of valvular heart disease of $\geq$ grade II. One experienced investigator blinded to the study performed all echocardiographic estimations.

Analysis of Heart Rate Variability

All subjects were monitored for 24 h before cardioversion, with all recordings obtained on an outpatient basis. Patients were advised to perform their routine daily activities. All subjects were asked to keep a diary for the registration period. Electrocardiographic recording was made using a cassette-based two-channel ECG recorder (Reynolds Tracker or Reynolds Sherpa, Reynolds Medical, Hertford, England). Electrode positions similar to V₁ and V₅ were used. The ECG signal was digitized and stored using a commercially available PC-based system (Aspect Holter System, Daltek, Borlänge, Sweden). An automatic analysis of arrhythmias was first made and the QRS complexes were classified. One experienced technician then manually checked all recordings. The following time domain measures were calculated: the standard deviation (SD) of all normal RR intervals in the entire 24-h ECG recording (SDRR); the SD of the mean of RR intervals for all 5 min segments of a 24-h ECG recording (SDARR), and the mean of the SDs of the RR intervals for each 5 min segment of a 24-h ECG recording (SDRR index). Values for the whole 24-h period, for the day (7.30–21.30) and the night (0.00–05.00) were calculated.

Statistical Analysis

Continuous variables are given as mean values $\pm$ SD. Univariate analysis for comparison of clinical characteristics was performed using unpaired *t*-tests, Wilcoxon, Mann-Whitney test, or a chi-square test if appropriate. Multivariate analysis (logistic regression) was applied for covariates in univariate

analysis with p values ≤ 0.20 . Odds ratio and 95% CI were calculated with standard methods. A p value < 0.05 was considered statistically significant. Calculations were performed with the statistical computer package Statistica 5.0 (StatSoft Inc., Tulsa, Oklahoma, USA).

The study was approved by the Local Ethics Committee of South Hospital and Karolinska Hospital, and patients gave their written, informed consent to participate.

Results

In all, 166 patients were included and underwent electric cardioversion. Mean age for the total group was 68 years (range 45–83). Mean duration of AF was 5 months (range 1–48), with only 4 patients with a duration of > 12 months. Unknown duration of AF was present in 50 (30%) patients. Echocardiographic assay and Holter ECG with acceptable quality for estimations were present in 151 and 148 patients, respectively.

Outcome of Direct Current Cardioversion

A total of 124 patients (75%) converted to sinus rhythm. Clinical characteristics of patients with and without conversion to sinus rhythm are presented in Table I. Only one patient relapsed into AF within the first hour after cardioversion; according to study protocol, this patient was defined as nonsuccessful cardioversion. However, this did not influence the results.

In univariate analysis, cardioversion success was dependent only on the patients' weight and BMI. Patients' age did not differ significantly between the two groups ($p < 0.08$), but with a trend toward a higher mean age for patients with conversion to sinus rhythm. Neither did mean duration of AF differ significantly between the two groups (excluding patients with unknown duration). After dividing the total group into patients with a duration of < 6 months versus patients with ≥ 6 months or unknown duration of AF, a significant difference was apparent. As shown in Table II, there were no significant differences in any of the measured echocardiographic data for patients with or without conversion to sinus rhythm. All di-

TABLE I Clinical characteristics of patients ($n=166$) with an unsuccessful versus successful electric cardioversion and atrial fibrillation versus sinus rhythm at 4 weeks after cardioversion

	AF after ECV ($n=42$)	SR after ECV ($n=124$)	p Value ^a	AF at 4 weeks ($n=120$)	SR at 4 weeks ($n=46$)	p Value ^a
Male	30 (71)	81 (65)	NS	81 (68)	30 (65)	NS
Age (years), mean (range)	66.2 (45–82)	69.1 (46–83)	0.08	68.6 (45–83)	67.8 (46–83)	NS
Weight (kg)	83.6 (12.9)	77.6 (11.9)	0.007	78.9 (12.7)	79.7 (11.8)	NS
BMI (kg/m^2)	27.2 (3.7)	25.9 (3.5)	< 0.04	26.4 (3.8)	25.8 (2.8)	NS
AF duration, months, mean (range)	6.6 (2–48)	4.6 (1–24)	0.09	5.2 (1–48)	4.6 (1–24)	NS
AF duration < 3 months	8 (19)	39 (31)	0.12	28 (23)	19 (41)	< 0.03
AF duration < 6 months	15 (36)	69 (56)	< 0.03	56 (47)	28 (61)	0.10
AF, unknown duration	16 (38)	34 (27)	0.19	39 (33)	11 (24)	NS
Associated disease ^b						
Hypertension	13 (31)	50 (40)	NS	38 (32)	25 (54)	< 0.01
Ischemic heart disease	5 (12)	19 (15)	NS	17 (14)	7 (15)	NS
Congestive heart failure	24 (57)	77 (54)	NS	74 (62)	27 (59)	NS
Valvular heart disease	10 (25)	29 (26)	NS	25 (23)	14 (34)	0.16
COPD	4 (10)	8 (6)	NS	11 (9)	1 (2)	0.12
Diabetes mellitus	3 (7)	6 (5)	NS	5 (4)	4 (9)	NS
Corrected thyroid disease	4 (10)	7 (6)	NS	8 (7)	3 (7)	NS
Lone AF ^c	17 (40)	36 (29)	0.17	44 (37)	9 (20)	0.03
Asymptomatic	17 (41)	35 (28)	0.14	38 (32)	14 (29)	NS
Digoxin	13 (31)	40 (32)	NS	40 (33)	13 (28)	NS
Beta blocker	11 (26)	42 (34)	NS	26 (22)	27 (59)	< 0.0001
Verapamil/diltiazem	5 (12)	12 (10)	NS	10 (8)	7 (15)	0.19
Calcium antagonist ^d	5 (12)	13 (10)	NS	11 (9)	7 (15)	NS
No rate control drug treatment	15 (36)	46 (37)	NS	51 (43)	10 (22)	< 0.01

Values are expressed as mean (standard deviation) or number (%) of patients.

^a p Value of univariate analysis. p Values > 0.20 are stated as NS (nonsignificant).

^b Percentages add up to $> 100\%$ because of coexistent diseases.

^c Defined as the absence of any of the above-mentioned diseases.

^d Long-acting dihydropyridin-derivates.

Abbreviations: AF = atrial fibrillation, SR = sinus rhythm, ECV = electric cardioversion, BMI = body mass index, COPD = chronic obstructive pulmonary disease.

TABLE II Echocardiographic characteristics of patients (n = 151) with an unsuccessful versus successful electric cardioversion and atrial fibrillation versus sinus rhythm at 4 weeks after cardioversion

	AF after ECV (n = 42)	SR after ECV (n = 124)	p Value ^a	AF at 4 weeks (n = 120)	SR at 4 weeks (n = 46)	p Value ^a
Left atrial size, parasternal view (mm) ^b	33.7 (2.9)	34.4 (3.5)	NS	34.3 (3.4)	34.0 (3.2)	NS
Left atrial area (mm ²) ^b	1.299 (177)	1.358 (235)	0.17	1.359 (229)	1.298 (198)	0.15
Right atrial area (mm ²) ^b	1.142 (168)	1.199 (225)	0.18	1.209 (216)	1.120 (194)	<0.03
LVEDd (mm) ^b	39.2 (3.9)	39.1 (4.7)	NS	39.2 (4.8)	39.0 (3.3)	NS
LV wall thickness (mm) ^b	7.7 (0.6)	8.3 (1.5)	0.06	8.3 (1.4)	7.8 (1.1)	0.10
Ejection fraction (%)	47.4 (6.2)	46.1 (6.5)	NS	46.5 (6.3)	46.1 (6.7)	NS
Wall motion score index	1.07 (0.23)	1.16 (0.31)	0.11	1.13 (0.29)	1.16 (0.31)	NS
Aortic stenosis	0	3 (3)	NS	1 (1)	2 (5)	NS
Aortic insufficiency	1 (2)	3 (3)	NS	2 (2)	2 (5)	NS
Mitral insufficiency	6 (15)	16 (15)	NS	15 (14)	7 (17)	NS
Tricuspid insufficiency	3 (8)	14 (13)	NS	12 (11)	5 (12)	NS

Values are expressed as mean (standard deviation) or number (%) of patients.

^a p Value of univariate analysis. p Values > 0.20 are stated as NS (nonsignificant).

^b All dimensions are corrected for BSA (body surface area).

Abbreviations: LVEDd = left ventricular end diastolic diameter, LV = left ventricular. Other abbreviations as in Table I.

mensions in Table II are corrected for BSA; however, calculations performed with uncorrected dimension did not change the results. None of the measured heart rate variability parameters (mean RR, SDRR, SDARR, SDRR index) was significantly different between patients with and without conversion to sinus rhythm.

In logistic regression analysis, only duration of AF < 6 months (p < 0.04, OR 2.2, 95% CI 1.1–4.7) and patients' weight (p < 0.03, OR 2.3, 95% CI 1.1–4.8 for weight < 80 kg) remained as independent predictors of success (Table III).

Clinical Characteristics Associated with Maintenance of Sinus Rhythm Four Weeks after Cardioversion

Clinical characteristics of all patients (n = 166) with AF or sinus rhythm at 4 weeks after cardioversion are presented in Table I. It should be noted that patients with failure to convert at cardioversion are included. At 4 weeks after cardioversion, 46 of 124 (37%) patients maintained sinus rhythm and 120 of 166 (72%) patients had AF.

In univariate analysis, maintenance of sinus rhythm was dependent on duration of AF < 3 months, presence of hypertension (with a better outcome for patients with hypertension), lone AF (with an adverse outcome for patients with lone AF), concomitant medication with beta blockers, or the absence of antiarrhythmic treatment (Table I). Of echocardiographic measurements, only a smaller right atrial area was a significant determinant for maintenance of sinus rhythm (Table II). None of the values measured with Holter ECG was significantly different between patients with and without relapse of AF.

In a logistic regression model, the presence of hypertension or lone AF disappeared as independent determinants for maintenance of sinus rhythm. This was explained by unequal

distribution of medication with beta blockers in these patients. The following parameters remained as significant determinants: AF < 3 months, treatment with beta blockers or verapamil/diltiazem, and a smaller right atrial area (Table III). Even a smaller right atrial dimension (medial-lateral diameter, four-chamber apical view) was an independent factor. However, right atrial area and dimension were significant only after adjusting for BSA.

We also separately analyzed determinants for maintenance of sinus rhythm, including only patients with sinus rhythm after cardioversion (n = 124). Of these patients, 78 (63%) relapsed into AF while 46 (37%) maintained sinus rhythm. In

TABLE III Multivariate analysis (logistic regression) of predictors for successful cardioversion and maintenance of sinus rhythm 4 weeks after electric cardioversion (n = 166)

	OR (95% CI)	p Value
Successful cardioversion		
AF duration < 6 months	2.2 (1.1–4.7)	<0.04
Weight < 80 kg	2.3 (1.1–4.8)	<0.03
Sinus rhythm after 4 weeks		
AF duration < 3 months	2.5 (1.1–5.6)	<0.04
Beta blocker	7.0 (3.0–16.3)	<0.00001
Verapamil/diltiazem	3.6 (1.1–12.1)	<0.04
Right atrial area < 1.300 mm ² ^a	10.1 (1.7–59.7)	<0.02
Right atrial dimension < 37 mm ^{a, b}	5.9 (1.4–25.4)	<0.02

^a Dimensions are corrected for BSA (body surface area).

^b Medial-lateral diameter in the apical four-chamber view.

Abbreviations: OR = odds ratio, CI = confidence interval, AF = atrial fibrillation.

logistic regression analysis, the results were consistent compared with analysis of all patients with one exception. In addition to AF < 3 months, treatment with beta blockers or verapamil/diltiazem, and a smaller right atrial area/right atrial dimension, long-acting-dihydropyridine Ca-antagonist was also an independent factor for maintenance of sinus rhythm ($p < 0.02$, OR 6.4, 95% CI 1.5–26.2). Thus, although verapamil/diltiazem and long-acting-dihydropyridine Ca-antagonist did not differ significantly in the univariate analysis (Table I), they were revealed to be significant independent factors in the multivariate analysis.

Discussion

This prospective study shows that, in persistent AF with a duration of > 1 month, patients' weight and short duration of AF are independent factors for successful cardioversion. Short duration of AF, treatment with beta blockers or verapamil/diltiazem, and right atrial area/right atrial dimensions are independent factors for maintenance of sinus rhythm.

The success rate at cardioversion in our study was 75%, which is in accordance with earlier studies.^{6–15} We found no significant difference in mean duration of AF between the two groups. Only after dividing patients into two groups with a duration of AF of more or less than 3 and 6 months, respectively, was the duration of AF found to be an independent factor. Most earlier studies have included patients with a duration of AF of < 1 month and > 12 months, which probably increases the probability that duration of AF is a significant determinant. In our study, there were only a few patients (4 of 166) with a duration of > 1 year. This probably reflects a bias in selection of patients for elective cardioversion, as these patients are considered to have a low success rate at cardioversion and maintenance of sinus rhythm. The reason for defining persistent AF in our study as a duration of AF for > 1 month is related to clinical practice. In patients with short duration of AF (e.g., < 1 month), most clinicians agree that an effort should be made to restore sinus rhythm. Moreover, adequate therapy with anticoagulation in patients with a duration of AF of > 2 days implies that elective cardioversion often will be delayed for several weeks (months).

We also included patients (30%) with unknown duration of AF. To our knowledge, there are no other studies evaluating these patients with regard to success rate at cardioversion and maintenance of sinus rhythm. The success rate for patients with unknown duration compared with patients with known duration was not significantly different (68 and 78%, respectively). Corresponding percentages for maintenance of sinus rhythm at 4 weeks were also not significantly different (22 and 30%, respectively). Since many of the often asymptomatic patients with unknown duration of AF may have an indication for life-long therapy with anticoagulation if not converted, our finding may justify an attempt to restore sinus rhythm in these patients.

Besides the duration of AF, the patients' weight was the only independent predictor for a successful cardioversion, a find-

ing that was not evaluated in most of the earlier studies. However, in the studies including weight as a clinical variable, obesity has been associated with an adverse outcome of cardioversion.²⁷ This is consistent with the probability that successful cardioversion depends on the amount of energy delivered to the heart and the higher efficacy of internal cardioversion.²⁸

In our study, patients' age did not influence success rate, which is in accordance with the results from the Working Group of Leading Hospital Cardiologists (ALKK) study including 1,152 patients with AF;¹⁵ neither did various parameters of echocardiographic measurements predict the outcome of cardioversion.

In contrast to most previous studies, our patients did not have treatment with drugs known to influence success rate or maintenance of sinus rhythm (e.g., class I and III). This is in agreement with clinical practice in patients with AF assigned to undergo their first electric cardioversion.^{29, 30} With this strategy, 60–80% of patients relapse into AF within 12 months.^{30, 31} In our study, 63% relapsed into AF within 1 month. This disappointing high relapse frequency may in part be explained by the fact that we did not include patients with short duration (< 1 month) of AF. Furthermore, earlier results are also based on the inclusion of patients with paroxysmal AF and atrial flutter.

A novel result was that, besides the duration of AF, treatment with beta blockers as well as verapamil/diltiazem were found to be independent factors for maintenance of sinus rhythm. In a study of Shenasa *et al.*, intravenous and oral administration of verapamil or diltiazem enhanced sustenance of electrically induced AF.³² In contrast, recent data from studies in a goat model have shown that preadministration of verapamil prevents electrical remodeling.³³ Moreover, in a study including 61 patients, the use of intracellular calcium-lowering drugs (beta blockers or calcium antagonists) before cardioversion (i.e., during AF) was an independent factor for maintenance of sinus rhythm after successful cardioversion.³⁴ Recently, DeSimone *et al.* demonstrated that pretreatment with verapamil before cardioversion reduces relapse of AF during the first week.³⁵

Prophylactic beta blocker administration to patients in sinus rhythm undergoing coronary artery bypass graft reduces the incidence of postoperative AF.³⁶ However, whether beta blockers prevent recurrence of AF after electric cardioversion remains to be proved in a prospective randomized study, which seems to be urgent in considering the high frequency of recurrence of AF and the risks of proarrhythmias with antiarrhythmic agents of class I and III.

Of echocardiographic variables, only a smaller right atrial area/dimension (medial-lateral diameter, four-chamber apical view) was an independent factor for maintenance of sinus rhythm. This was significant only after adjusting for BSA, indicating that the crucial factor is the relative enlargement of the atrium and not the atrial dimension per se, and that right atrial dimension, in absence of mitral valvular disease, is a more sensitive predictor than left atrial dimension. Earlier studies show conflicting results regarding the predictive value of atrial enlargement. Some studies have shown increased risk

of recurrence of AF with atrial enlargement,^{8, 10, 37} whereas others have not.^{7, 9, 11–15} However, most of these studies have only measured left atrial dimension,^{8–10, 12–15, 37} and none of them has performed adjustment for BSA. Our results may have been influenced by the fact that there were only a few patients (4 of 166) with a left atrial dimension of >50 mm (parasternal view). This is probably a selection bias partly related to the low number of patients with a duration of AF > 12 months included in our study.

Limitations

The use of paddles instead of patches results in an inconsistency in paddle pressure that may contribute to outcome.

The lack of a standardized number of countershocks at 360 J may have influenced our results, since repeated countershock has been shown to decrease transthoracic resistance.²⁷ However, since there were no prescribed upper limits, a comparison between patients with or without success at cardioversion would thereby by necessity show a higher total amount of energy in the latter patients.

Conclusion

In patients with persistent AF, their weight and the duration of AF are independent factors for a successful cardioversion. The duration of AF, treatment with beta blockers or verapamil/diltiazem, and right atrial area/dimension are independent factors for maintenance of sinus rhythm.

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