Comparison of Rate and Rhythm Control in Hypertension Patients With Atrial Fibrillation

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Background Atrial fibrillation (AF) is a very common cardiac arrhythmia, and is associated with an increased mortality in patients with hypertension. Whether the best therapeutic approach for these patients is to restore sinus rhythm (SR) or to adequately control the ventricular rate is still controversial. The aim of this study is to compare both strategies in patients with hypertension.

Methods and Results Two hundred and twenty-one patients with hypertension and AF of duration >48 h were randomly assigned to either the rhythm (n=155) or rate (n=66) control group. Exercise capacity was improved in the rhythm control group in the 1st year of the study ($p<0.0001$). There were no statistically significant differences in the embolic event rate and the total mortality between the 2 groups at the end of the study ($p=NS$).

Conclusions Although restoring and maintaining SR had a beneficial effect on exercise capacity in patients with hypertension and AF, no significant difference was found in terms of the total mortality and the embolic event rates. Thus, rate control is an acceptable primary strategy in patients with AF and hypertension. (Circ J 2008; 72: 705–708)

Key Words: Atrial fibrillation; Cardioversion; Hypertension

Atrial fibrillation (AF) is the most frequent reason for hospital admission and is also the most common sustained cardiac arrhythmia, occurring in 0.4% of the adult population.^{1,2} Its prevalence is age-related and increases significantly to 1–4% after 60 years of age.^{1–3} Owing to the age structure of Turkey's population and the increasing morbidity and comorbidity, one must assume that this arrhythmia will reach an even higher prevalence. AF is associated with a significantly higher risk of systemic embolism, congestive heart failure and death.^{1–4}

AF and hypertension are 2 prevalent, and often coexisting, conditions in the adult population.^{5–7} Their incidence increases with age, and they are responsible for considerable morbidity and mortality.^{5,6}

The purpose of the present study was to determine whether a strategy that attempts to restore and maintain sinus rhythm (SR) in AF will improve survival and exercise capacity among patients with hypertension.

Methods

Patients aged >18 years who had hypertension and persistent AF for >48 h were included in the study. AF was defined as having: an absence of P-waves, coarse or fine fibrillatory waves, and completely irregular R-R intervals.

The diagnosis of essential hypertension was defined as having BP >140/90 mmHg, or current use of antihyperten-

sive drugs, according to the guidelines of the 1999 World Health Organization–International Society of Hypertension (WHO/ISH) Committee.⁸

Patients suffering from valvular heart diseases, coronary artery disease, heart failure, thyroid disease, renal failure, sick sinus syndrome, pulmonary embolism, acute pericarditis, diabetes mellitus, chronic obstructive lung disease, hypertrophic obstructive cardiomyopathy and atrial thrombus were excluded from the study.

The patients were randomly assigned to either the rhythm control group or rate control group. The patients were kept under observation for a minimum follow-up period of 3 years, with regular weekly visits in the 1st month and then once a month thereafter. The composite endpoints of the study were embolism, death and exercise capacity for both groups.

At baseline, resting 12-lead ECG was obtained, and transthoracic echocardiography (TTE), transesophageal echocardiograph (TEE) and exercise tests were performed. At every control visit, a 12-lead ECG was taken. At the end of the 1st year all patients underwent exercise testing.

The TTE and TEE studies were performed with an Acuson 128 XP/5 ultrasound system. M-mode TTE was used to measure the left atrial dimension at end-systole and the LVEF, according to the recommendations of the American Society of Echocardiography. Food consumption was stopped at least 4 h before the TEE was done. Patients received local pharyngeal anesthesia (1% lidocaine spray) as the only premedication, and were given effective anticoagulation either with heparin or warfarin (INR levels 2.0–3.0 or APTT 2 times control, 60–80 s) before the TEE. Patients in whom the TEE did not detect any thrombus were cardioverted to SR. For cardioversion (CV), amiodarone (administered intravenously (iv)) was used (300 mg over 1 h, then 15–20 mg/kg for the remaining 23 h). If CV was not achieved after iv loading, electrical CV was attempted.

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Fig 1. Treatment outcomes. Of the 221 patients enrolled in the study, 169 were assigned to the rhythm control group and 52 to the rate control group. Note that 14 patients who were not successfully cardioverted were added to the rate control group. By the end of the follow-up period, 2 deaths and 4 thromboembolic events, and 5 deaths and 8 thromboembolic events were seen in the rhythm control and in the rate control group, respectively. AF, atrial fibrillation; TEE, transesophageal echocardiograph.

Electrical CV was started with 200 J, repeated if necessary and then tried again with 360 J. The procedure was brought to an end after the restoration of SR or 2 attempts at 360 J. All patients in the rhythm control group received amiodarone (200mg q.i.d) during the follow-up period.

To detect early recurrence of arrhythmia, electrocardiographic monitoring was performed in all patients during the 1st 24h of their stay in hospital. SR lasting more than 24h was judged to be successful CV.

Anticoagulation (warfarin, INR ratio 2.0–3.0) was given to all patients in the rate control group during the study period but was discontinued in the rhythm control group after the 1st month of CV.

Patients were treated with calcium antagonists, angiotensin-converting enzyme inhibitors (ACEI) and β -blockers, as needed. Patients intolerant to ACEIs were given angiotensin-II receptor antagonists (eg, losartan). For rate control, digoxin, verapamil and metoprolol were used. The target heart rate was <80 beats/min at rest.

Exercise capacity was determined during symptom-limited exercise tests. All patients underwent treadmill exercise testing twice, which was adjusted according to the modified Bruce protocol, 1st before CV and second at the end of the 1st year of the study. Fatigue and dyspnea were the 2 major symptoms that necessitated exercise testing to be discontinued.

Statistical Analysis

Differences between the 2 groups were detected using ANOVA, chi-square test and Student's t-test. Kaplan–Meier analysis was performed to estimate the cumulative rates of survival and embolic events. In all cases, a p-value of ≤ 0.05 was considered statistically significant.

Table 1 Baseline Characteristics of the 2 Groups

	Rhythm control	Rate control	p value
No. patients	155	66	
Age (years)	61 $\pm$ 9	57 $\pm$ 11	NS
Female (%)	80 (51.7%)	33 (50%)	NS
Male (%)	75 (48.3%)	33 (50%)	NS
Duration of AF (months)	11 $\pm$ 7	13 $\pm$ 6	NS
LVEF (%)	60 $\pm$ 11	63 $\pm$ 9	NS
LA dimension (cm)	4.4 $\pm$ 1.5	4.9 $\pm$ 1.1	NS
LVEDD (cm)	5.2 $\pm$ 0.5	4.9 $\pm$ 1.1	NS
Exercise duration (min)	7.1 $\pm$ 2.7	6.6 $\pm$ 1.3	NS
MET value	5.3 $\pm$ 1.4	4.9 $\pm$ 1.8	NS
Resting heart rate (beats/min)	110 $\pm$ 17	111 $\pm$ 24	NS
1 st stage heart rate (beats/min)	150 $\pm$ 26	154 $\pm$ 22	NS
Peak heart rate (beats/min)	180 $\pm$ 21	182 $\pm$ 27	NS

Values are presented as the mean $\pm$ SD.

NS, not significant; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; MET, multiples of oxygen consumption at rest.

Table 2 Clinical Outcomes Between 2 Groups at the End of the Study

	Rhythm control	Rate control	p value
All embolic events (%)	4 (6%)	8 (12%)	NS
Cerebral embolism (%)	2 (3%)	2 (3%)	NS
TIA (%)	2 (3%)	4 (6%)	NS
Peripheral embolism (%)	0	2 (3%)	NS
Death from all causes (%)	2 (3%)	5 (7%)	NS
Embolic death (%)	1 (1%)	2 (3%)	NS
Pump failure death (%)	0	1 (1%)	NS
Sudden death (%)	1 (1%)	2 (3%)	NS

TIA, transient ischemic attack. Other abbreviation see in Table 1.

Results

A total of 221 patients, without thrombus in the left atrium, as determined by TEE, were randomly assigned to either the rhythm control (n=155) or rate control (n=66) groups. Fourteen patients who could not be cardioverted were added to the rate control group (resulting in 155 patients in the rhythm control group and 66 patients in the rate control group; Fig 1).

The average age of the patients was 61 $\pm$ 9 and 57 $\pm$ 11 years in the rhythm and rate control groups, respectively (p=NS). The average follow-up period was 39 $\pm$ 21 and 40 $\pm$ 19 months in the rhythm and rate control groups, respectively (p=NS).

Baseline characteristics with regard to the duration of AF, and echocardiographic and exercise parameters were similar in both groups (Table 1). There were no differences between exercise duration, resting, first-stage and peak heart rates between the 2 groups at baseline.

Of 169 patients with AF, 155 (91.7%) were successfully cardioverted to SR. Fourteen patients who could not be cardioverted were then included in the rate control group. No thromboembolic events occurred in hospital.

One hundred and twenty-one patients (54.7%) completed the 3-year follow-up study. In the rhythm control group, 62 patients (40%) were in SR at the end of the follow-up period. All of the patients were in AF in the rate control group at the end of the 3-year follow-up period.

The embolic event rates and the overall mortality of the patients in both groups were similar at the end of the study

Fig2. Cumulative probability of survival is shown.

Fig3. Cumulative probability of embolic events is shown.

Table 3 Comparing Exercise Test Parameters in the Rhythm Control Group at the End of the 1st Year

	Baseline	At 1 year	p value
Exercise duration (min)	7.1±2.7	9.1±2.7	<0.0001
MET value	5.3±1.4	6.3±1.4	0.0005
Resting heart rate (beats/min)	110±17	84±8	0.0007
1 st stage heart rate (beats/min)	150±26	104±11	<0.0001
Peak heart rate (beats/min)	180±21	146±21	<0.0001

Values are presented as the mean ± SD.

Abbreviations see in Table 1.

Table 4 Comparing Exercise Test Parameters in the Rate Control Group at the End of the 1st Year

	Baseline	At 1 year	p value
Exercise duration (min)	6.6±1.3	7.1±2.1	NS
MET value	4.9±1.8	5.5±2.0	NS
Resting heart rate (beats/min)	111±24	89±15	<0.0001
1 st stage heart rate (beats/min)	154±22	138±18	<0.0001
Peak heart rate (beats/min)	182±27	168±28	0.0041

Values are presented as the mean ± SD.

Abbreviations see in Table 1.

(Table 2; Figs 2,3). There were 2 deaths (3.22%) in the rhythm control group and 5 deaths (7.57%) in the rate control group ($p=NS$). There were 4 embolic events (6.45%) in the rhythm control group and 8 embolic events (12.12%) in the rate control group ($p=NS$) (Figs 2,3). At the time of the embolic events, 3 patients from the rhythm control group were in AF and 1 patient was in SR.

There were significant differences between the 2 treatment strategies with respect to exercise capacity, as measured by exercise duration, at the end of the 1st year ($p<0.0001$; Tables 3,4). Although the duration of exercise had increased in both treatment groups, it was statistically significant only in the rhythm control group ($p<0.0001$; Tables 3,4).

No major bleeding occurred in either of the groups. By the end of the follow-up period, 4 minor (6.06%) bleeding cases and 1 (1.61%) minor bleeding case was observed in

the rate control group and the rhythm control group, respectively.

Discussion

AF is the most common sustained arrhythmia encountered in clinical practice!³ The incidence of AF rises progressively with age from 0.5% for the 50–59-year age group to almost 9% for the 80–89-year age group⁹ AF is also a major cause of stroke in the elderly!¹⁰ and is responsible for 7–31% of all ischemic strokes!¹¹ Studies have shown that 50–70% of patients with stroke associated with AF, died or had a severe permanent neurologic deficit!^{12,13} Also, it is associated with increased risk of mortality and cardiovascular events!¹⁴

Hypertension is a major cause of non-rheumatic AF!¹⁵ In patients with hypertension, the risk of AF increases with age

and left ventricular mass.⁵ The prognostic value of hypertension in AF is somewhat conflicting.

Advantages of restoring SR in cases with AF include a marked relief of symptoms, improved cardiac hemodynamics and a decrease in the number of thromboembolic events.^{3,10}

The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control Versus Electrical Cardioversion (RACE) studies showed that the risk of embolism and the relief of symptoms does not decrease after restoring SR.^{16–21}

In the AFFIRM study, patients who had at least 1 other risk factor for stroke and death were randomly assigned to either the rate or rhythm control group.^{16–21} In that trial, risk factors were: being aged ≥ 65 years, having systemic hypertension, diabetes mellitus, congestive heart failure, transient ischemic attack, prior stroke, left atrium ≥ 50 mm, and left ventricular fractional shortening of $<25\%$ or left ventricular ejection fraction of <0.40 . Hypertension was present in 71% of participants in the AFFIRM trial. Patients were followed up for approximately 5 years and no difference was found in terms of stroke and mortality between the 2 groups. Most of the strokes occurred in patients whose warfarin therapy was stopped or with an INR of <2.0 . Thus, anticoagulation was recommended to all patients with risk factors for stroke. It was concluded that the primary treatment in AF should be the rate control.

In the RACE trial, 512 patients with AF of >24 h but <1 year duration were randomly assigned to either the rate control or rhythm control group, and followed for 3 years.^{19–20} At the end of the study, it was shown that rhythm control was not superior to rate control, and that rate control should be the preferred treatment for those patients with high risks for recurrence or potential risks with antiarrhythmic treatment and, especially, for patients with hypertension.

The previous 2 studies showed that the CV of patients with high risk for stroke provided no benefit over rate control, so rate control was established as the primary therapy for this group of patients.

Also, in the Strategies of Treatment in Atrial Fibrillation (STAF) trial no difference was found in terms of morbidity and mortality among patients with AF who were randomly assigned to the rate or rhythm control group.²²

For patients with AF, it is important to recognize that improved exercise tolerance is just as important as improved survival. So, one of the goals of therapy for AF should be to improve patients' exercise tolerance. The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial showed that rhythm control leads to better exercise tolerance compared with rate control,²³ which is in agreement with the result of the present study. Symptomatic AF is one of the indications to restore SR.

In conclusion, although patients with AF and hypertension receive considerable benefits from the restoration of SR in terms of exercise capacity, no significant difference was found in terms of the mortality and embolic event rates. Thus, rate control is an acceptable primary strategy for asymptomatic patients with AF and hypertension.

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