Comparison of Rate and Rhythm Control in Patients With Atrial Fibrillation and Nonischemic Heart Failure

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SUMMARY

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

One hundred and fifty-four patients with AF duration greater than 48 hours and nonischemic left ventricular dysfunction were randomized either to a rhythm (n = 84) or rate (n = 74) control group. The composite end points of the study were embolism, death, and exercise capacity.

The average age of the patients was 61 ± 10 years in the rhythm control group and 58 ± 12 years in the rate control group (P = NS). The average follow-up period was 35 ± 21 months in the rhythm control group and 37 ± 19 months in the rate control group (P = NS). In the first year of the study, exercise capacity and left ventricular ejection fraction (LVEF) were improved in the rhythm control group compared to the exercise capacity and LVEF of the rate control group ($P < 0.0001$ and $P = 0.0005$, respectively).

There were no statistically significant differences in the embolic event rate between the two groups (P = NS). The mortality rate, especially for death due to pump failure, was significantly higher in the rate control group at the end of the study ($P < 0.0001$).

Restoring and maintaining sinus rhythm had a beneficial effect on mortality and exercise capacity in patients with nonischemic heart failure and AF. (Jpn Heart J 2004; 45: 591-601)

Key words: Atrial fibrillation, Heart failure, Cardioversion, Prognosis

ATRIAL fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 0.4% of the adult population.[1)] Its prevalence is age-related and increases significantly to 1% to 4% after 60 years of age.[1,2)] AF is associated with a significantly higher risk of systemic embolism, congestive heart failure, and death.[1-3)]

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The risk of developing AF appears to be 5-10 times higher in patients with chronic heart failure.[4] AF is present in 10% to 50% of patients, with the highest incidence among those with the most severe heart failure.[5-7] The prevalence of AF in patients with heart failure increases from 4% in NYHA class I to 50% in those with NYHA class IV.[8] The development of AF in heart failure appears to independently predict mortality from pump failure or any other cause.[9-12] However, it is not clear whether restoration and maintenance of sinus rhythm will improve survival and exercise capacity in patients with heart failure.

The purpose of this study was to determine whether a strategy that attempts to restore and maintain sinus rhythm will improve survival and exercise capacity among patients with nonischemic cardiomyopathy.

METHODS

Patients older than 18 years of age who had persistent AF lasting more than 48 hours and nonischemic left ventricular dysfunction diagnosed by echocardiography (EF < 50%) and coronary angiography (normal coronary arteries) were included in the study. AF was defined as the absence of P waves, course or fine fibrillatory waves, and completely irregular RR intervals.

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

The patients were randomized 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 first month and then once a month thereafter. The composite end points of the study were embolism, death, and exercise capacity in both groups. Cause of death was classified as progressive heart failure, embolism, or sudden cardiac death.

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

The TTE and TEE studies were performed with an Acuson 128 XP/5 ultrasound system. M-mode TTE was used to measure left atrial (LA) dimension at end-systole and the LVEF according to the recommendations of the American Society of Echocardiography.[13] Food consumption was discontinued at least 4 hours before TEE. 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 seconds) before TEE. Patients without any detectable thrombus in TEE and who were randomized to the rhythm control group were cardioverted to sinus rhythm. For cardioversion (CV) IV amiodarone was used (300 mg over 1 hours, then 15-20 mg/kg for the remaining 23 hours). If CV was not achieved after IV loading, electrical CV was attempted. Electrical CV started with 200 joules (J), repeated if necessary and then tried again with 360 J. The procedure was brought to an end after the restoration of sinus rhythm or two attempts at 360 J. All patients in the rhythm control group received amiodarone (200 mg q.i.d) during the follow-up period.

To detect the early recurrence of arrhythmia, electrocardiographic monitoring was performed in all patients during the first 24 hours in the hospital. Sinus rhythm lasting more than 24 hours was judged to be successful CV.

Anticoagulation therapy (warfarin, INR ratio 2.0-3.0) was given to all patients in the rate control group during the study period and was discontinued in the rhythm control group after the first month of CV.

Although the patients were given digoxin, a diuretic, or an aldesterone antagonist as needed, they were mainly required to be on an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) and β-blocker (metoprolol) if there were no contraindications. Patients intolerant to ACE inhibitors were administered an angiotensin-II receptor antagonist (losartan).

Digoxin and metoprolol were used for rate control. Target heart rate was less than 80 beats per minute at rest. Initially, 6.25 mg of metaprolol was given twice a day, and then increased to a maximum of 50 mg twice a day to achieve the target heart rate.

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, first before CV and secondly at the end of the first year of the study. Fatigue and dyspnea were the two major symptoms that necessitated discontinuation of the exercise test.

Statistical analysis: Differences between the two groups were determined with the chi-square test and Student's *t* test. In all cases, a P value ≤ 0.05 was considered statistically significant.

RESULTS

One hundred and fifty four patients, without thrombus in LA detected by TEE, were randomized to either the rate control ($n = 84$) or rhythm control ($n = 70$) groups.

The average age of the patients was 61 ± 10 years in the rhythm control group and 58 ± 12 years in the rate control group (P = NS).

The average follow-up period was 35 ± 21 months in the rhythm control group and 37 ± 19 months in the rate control group (P = NS).

Seventy of 80 patients (87.5%) with AF were successfully cardioverted to sinus rhythm. Ten patients who could not be cardioverted were included in the rate control group. No thromboembolic events occurred in the hospital.

One hundred and seventeen patients completed (76%) the 3-year follow-up period. In the rhythm control group, 33 patients (47%) were in sinus rhythm at the end of the study (Figure 1).

The baseline characteristics, including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, AF duration, concominant drug treatment, with the exception of digoxin ($P < 0.0001$), and echocardiographic and exercise parameters were similar in both groups (P = NS, Tables I, II).

There were no differences between resting, 1st stage, and peak heart rates between the two groups at the end of the first year (P = NS; Table III). There were significant differences between the two treatment strategies with respect to exercise capacity measured by exercise duration at the end of the first year ($P < 0.0001$; Table III). Although the duration of exercise increased in both treatment groups, it was statistically significant only in the rhythm control group ($P < 0.0001$; Tables IV, V). Similarly, the EF increase was more significant in the rhythm control group, compared to the rate control group ($P = 0.0023$; Tables IV, V). Heart rate was quite well controlled in both groups with respect to baseline values ($P < 0.0001$; Tables IV, V).

The overall mortality of patients in the rate control group was higher than that in the rhythm control group (Table VI). There were 6 deaths (16%) in the rhythm control group in comparison to 36 deaths (43%) in the rate control group ($P < 0.0001$). Progressive heart failure was responsible for most of the deaths in the rate control group ($P = 0.0002$). There were 6 embolic events (9%) in the rhythm control group and 9 embolic events (11%) in the rate control group (P = NS). In the rhythm control group, all of the strokes occurred after warfarin was stopped.

No major hemorrhaging occurred in either group although 5 minor bleeding cases (6%) were observed in the rate control group. No adverse event was seen with the use of amiodarone.

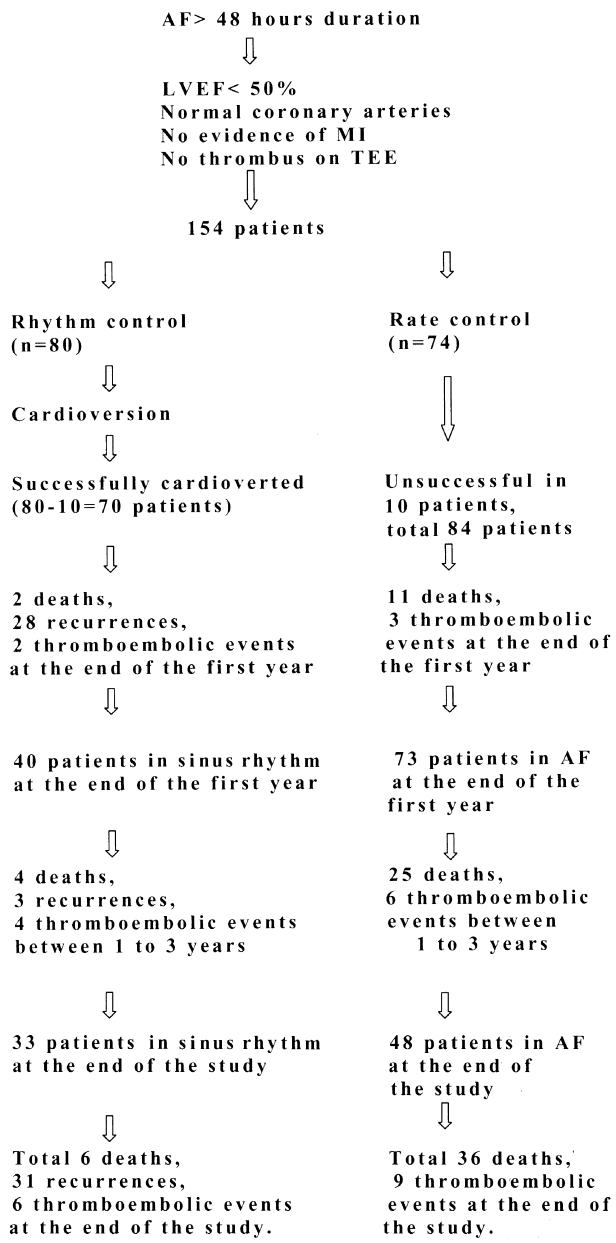


Figure 1. Treatment outcomes. Of the 154 patients enrolled in the study, 80 were assigned to the rhythm control group and 74 to the rate control group. Ten patients who were not successfully cardioverted were added to the rate control group. At the end of the first year 40 patients and at the end of the study 33 patients were in sinus rhythm in the rhythm control group. In the rhythm control group 6 deaths and 6 thromboembolic events and in the rate control group 36 deaths and 9 thromboembolic events were seen at the end of the study.

Table I. Baseline Characteristics of the Two Groups

	Rhythm control	Rate control	*P* value
Number of patients	70	84	
Age (years), mean ± SD	61 ± 10	58 ± 12	NS
Female (%)	24 (34%)	27 (32%)	NS
Male (%)	46 (66%)	57 (68%)	NS
Hypertension (%)	33 (47%)	45 (54%)	NS
Diabetes (%)	9 (13%)	15 (18%)	NS
Chronic obstructive pulmonary disease (%)	3 (4%)	9 (11%)	NS
History of thromboembolism (%)	3 (4%)	6 (7%)	NS
Duration of AF (months), mean ± SD	11 ± 7	13 ± 6	NS
LVEF (%), mean ± SD	31 ± 8	33 ± 15	NS
LA dimension (cm), mean ± SD	4.5 ± 1.5	4.7 ± 1.7	NS
LVEDD (cm), mean ± SD	5.9 ± 1.1	6.2 ± 1.4	NS
Exercise duration (minutes), mean ± SD	6.5 ± 2.9	6.8 ± 2.5	NS
MET value, mean ± SD	5 ± 1.7	5.2 ± 1.3	NS
Resting heart rate (beat/minutes), mean ± SD	92 ± 20	95 ± 16	NS
1st stage heart rate (beat/minutes), mean ± SD	127 ± 14	129 ± 11	NS
Peak heart rate (beat/minutes), mean ± SD	158 ± 22	164 ± 24	NS

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

Table II. Other Medications Taken by the Study Patients

	Rhythm control	Rate control	*P* value
Digoxin (%)	3 (4%)	65 (89%)	$P < 0.0001$
Diuretic (%)	35 (50%)	41 (49%)	NS
β-Adrenergic blocker (%)	38 (54%)	49 (58%)	NS
ACEİ (%)	54 (77%)	73 (87%)	NS
α-II receptor blocker (%)	16 (23%)	11 (13%)	NS
Amlodipine (%)	25 (36%)	33 (39%)	NS
Spironolactone (%)	45 (36%)	51 (61%)	NS

ACEİ = angiotensin converting enzyme inhibitor; NS = not significant.

Table III. Comparison of Echocardiographic and Exercise Test Parameters Between Two Groups at One Year

	Rhythm control	Rate control	*P* value
Number of patients	40	73	
LVEF (%), mean ± SD	38 ± 15	34 ± 15	NS
LA dimension (cm), mean ± SD	4.3 ± 0.6	4.9 ± 0.5	< 0.0001
LVEDD (cm), mean ± SD	5.9 ± 1.2	5.9 ± 0.5	NS
Exercise duration (minutes), mean ± SD	9.1 ± 2.5	7.3 ± 1.3	< 0.0001
MET value, mean ± SD	6.3 ± 1.5	5.4 ± 0.9	< 0.0001
Resting heart rate (beat/minutes), mean ± SD	82 ± 10	81 ± 9	NS
1st stage heart rate (beat/minutes), mean ± SD	95 ± 12	100 ± 16	NS
Peak heart rate (beat/minutes), mean ± SD	154 ± 18	153 ± 18	NS

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

Table IV. Comparison of Echocardiographic and Exercise Test Parameters at One Year in the Rhythm Control Group

	Baseline	At one year	*P* value
Number of patients	40	73	
LVEF (%), mean ± SD	31 ± 8	38 ± 15	0.0023
LA dimension (cm), mean ± SD	4.5 ± 1.6	4.3 ± 0.6	NS
LVEDD (mm), mean ± SD	5.9 ± 1.1	5.9 ± 1.2	NS
Exercise duration (min), mean ± SD	6.5 ± 2.9	9.1 ± 2.6	< 0.0001
MET value, mean ± SD	5 ± 1.6	6.3 ± 1.5	< 0.0001
Resting heart rate (beat/minutes), mean ± SD	92 ± 20	82 ± 10	0.024
1st stage heart rate (beat/minutes), mean ± SD	127 ± 14	95 ± 12	< 0.0001
Peak heart rate (beat/minutes), mean ± SD	158 ± 22	154 ± 18	NS

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

Table V. Comparison of Echocardiographic and Exercise Test Parameters at One Year in the Rate Control Group

	Baseline	At one year	*P* value
Number of patients	40	73	
LVEF (%), mean ± SD	33 ± 15	34 ± 15	NS
LA dimension(cm), mean ± SD	4.7 ± 1.8	4.9 ± 0.5	NS
LVEDD (mm), mean ± SD	6.1 ± 1.4	5.8 ± 0.5	NS
Exercise duration (min), mean ± SD	6.8 ± 2.4	7.3 ± 1.3	NS
MET value, mean ± SD	5.2 ± 1.3	5.4 ± 0.9	NS
Resting heart rate (beat/minues), mean ± SD	95 ± 16	81 ± 9	< 0.0001
1st stage heart rate (beat/minutes), mean ± SD	129 ± 11	100 ± 16	< 0.0001
Peak heart rate (beat/minutes), mean ± SD	164 ± 24	153 ± 18	= 0.0015

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

Table VI. Clinical Outcomes of the Two Groups at the End of the Study

	Rhythm control	Rate control	*P* value
Number of patients	39	84	
All embolic events (%)	6 (15%)	9 (11%)	NS
Cerebral embolism (%)	2 (33%)	3 (33%)	NS
TIA (%)	3 (50%)	4 (44%)	NS
Peripherial embolism (%)	1 (17%)	2 (22%)	NS
Death from all causes (%)	6 (15%)	36 (43%)	< 0.00001
Embolic death (%)	2 (33%)	3 (8%)	NS
Pump failure death (%)	3 (50%)	28 (78%)	0.00002
Sudden death (%)	1 (17%)	5 (14%)	NS

TIA = transient ischemic attack; NS = not significant.

DISCUSSION

AF is a common arrhythmia in patients with heart failure.[4-12] Despite the potentially adverse hemodynamic effect, the prognostic value of AF in heart failure is somewhat conflicting. Middlekauff and colleagues showed increased mortality in patients with advanced chronic heart failure and AF, as compared to those with sinus rhythm.[9] A substudy from Studies of Left Ventricular Dysfunction (SOLVD) showed that AF was associated with an increased risk for all-cause mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction.[10] The Digitalis Investigation Group (DIG) Trial also demonstrated increased mortality among patients with supraventricular tachyarrhythmias including AF.[11] Wang and colleagues reported a poor prognosis in patients with heart failure and AF in the Framingham Study Group.[12]

On the other hand, two extensive studies showed that in patients with moderate to severe chronic heart failure, the presence of AF had no effect on mortality. In the Vasodilator in Heart Failure Trial (V-Heft) performed with patients with moderate heart failure, increases in the rates of sudden death and total mortality were not significant in patients with AF and those in sinus rhythm.[6] Crijns and colleagues found that the presence or the development of AF in patients with advanced heart failure was not related to an adverse outcome during a mean follow-up of 3.4 years.[14]

In 2002, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control Versus Electrical Cardioversion (RACE) trials demonstrated no significant differences in mortality between strategies of rate control and rhythm control in patients with AF.[15,16] It was concluded that the primary treatment in AF should be rate control. 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 rate or rhythm control.[17] The results of these trials suggest the continuation of anticoagulation even if the sinus rhythm is restored.[18] We also observed in our study that all of the strokes occurred after warfarin was stopped in the rhythm control group. Therefore, we suggest that patients with heart failure should continue receiving warfarin therapy even if the maintenance of sinus rhythm is achieved.

The AFFIRM, RACE, and STAF trials were not primary studies aiming to establish the optimal management of AF in patients with heart failure.[15-17] However, there are only a few studies suggesting interventions to maintain sinus rhythm in heart failure. In the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) study, lower mortality was observed in patients who were converted to sinus rhythm with amiodarone.[7] Similarly, among patients enrolled in the Danish Investigators of Arrhythmia and Mortality ON

Dofetilide (DIAMOND) study, restoration of sinus rhythm with dofetilide in patients with left ventricular dysfunction was associated with a significant reduction in mortality and rate of hospitalization.[18] Azpitarte and colleagues observed an improvement in left ventricular systolic function in patients with heart failure, who were converted and sustained in sinus rhythm.[19] Brignole, *et al* randomized 66 patients with chronic AF, either to drug therapy for rate control or ablation and insertion of a VVIR pacemaker.[20] After 12 months they observed improvements in both groups in terms of quality of life and cardiac performance.

A reduction in heart rate is thought to be the principal mechanism implicated in the improvement of LV function. Rate control is considered adequate when it ranges between 60 and 80 beats per minute at rest and between 90 to 115 beats per minute during moderate exercise.[2] The mean ventricular rate at rest, achieved in our patients, was well within the range considered to be adequate. We also showed that heart rate was well controlled with exercise at the end of the first year.

It is important to recognize that in patients with advanced heart failure, exercise tolerance is as important as improved survival.[21] Therefore, one of the goals of therapy for AF in heart failure should be to improve exercise tolerance. The PIAF trial[21] showed that rhythm control compared with rate control, leads to better exercise tolerance, as we observed in our study.

The most important limitation of our study was the inability to exclude other factors which might improve LV function. Several drugs such as digoxin, ACE inhibitors, and β-blockers may improve LV function. However, since patients in both groups were taking these drugs, the limitation was minimal. We cannot rule out the possibility of recovery of LV function after subclinical myocarditis or better control of hypertension. In addition to restoring and maintaining sinus rhythm, amiodarone can also increase LVEF and improve exercise capacity and decrease survival in heart failure.[7]

It is concluded that patients with chronic AF and nonischemic left ventricular systolic dysfunction might benefit considerably from sinus rhythm restoration in terms of mortality and exercise capacity. Although the results of the ongoing Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Study may provide us with further information about rhythm or rate control in patients with AF with heart failure, we recommend CV as the optimal treatment strategy for patients with AF and nonischemic left ventricular systolic dysfunction.

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