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The effect of rate versus rhythm control strategy on the left ventricular function in patients with persistent atrial fibrillation: results of one year follow-up

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Abstract

Background: *Patients with persistent atrial fibrillation (AF) can be managed with either rhythm or rate control strategy. The restoration and maintenance of the sinus rhythm is not superior to the rate control regarding the total mortality and the rate of thromboembolic complications. Data concerning the effect of these strategies on left ventricular morphology and function is missing. The objective of our prospective randomised multicenter study in patients with persistent AF was to evaluate the effect of these two approaches on left ventricular morphology and function.*

Methods and Results: *The study group consisted of 205 patients (F/M 71/134; mean age 60.8 ± 11.2 years), including 101 patients randomized to the rate control approach (Group I) and 104 patients randomized to sinus rhythm (SR) restoration with DC cardioversion and subsequent antiarrhythmic drug treatment (Group II). Mean duration of AF was 231.8 ± ± 112.4 days. At the end of follow-up (12 months), SR was present in 64% of patients in Group II. Echocardiographic examination was performed at a baseline and at 2 and 12 months. The comparison of the left ventricular end-diastolic diameter revealed no difference within and between groups (50.8 ± 5.6 mm vs. 52.2 mm ± 6.8 mm at a baseline and 50.0 ± 6.0 vs. 52.0 ± ± 7.4 mm at 12 months, respectively). Overall, the fractional shortening of the left ventricle increased during the follow-up. Thus, the initial significant difference between groups (32.8 ± 6.6% vs. 29.9 ± ± 6.9%, $p < 0.005$) became insignificant at 12 months (35.6 ± 7.4% vs. 31.3 ± 7.3%).*

Conclusions: *We found no significant difference regarding the left ventricular morphology and function between the rate and rhythm control strategies in patients with persistent AF.* (Folia Cardiol. 2006; 13: 331–337)

atrial fibrillation, left ventricular function, rhythm control, rate control, echocardiography

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Introduction

Impaired left ventricular systolic function seen in atrial fibrillation (AF) seems to result from three major causes. The atrial arrhythmia inevitably leads to the loss of mechanical atrial function, adversely affecting left ventricular (LV) end-diastolic filling. In addition, abnormally fast ventricular rate in AF may have an adverse effect on the contractility, particularly in patients with underlying LV damage [1]. Finally, there is data suggesting the significant effect of the variable duration of ventricular diastolic filling on ventricular systolic function, independent of the lack of atrial contribution in diastolic filling and increased ventricular rate [2, 3]. These mechanisms lead to the decrease of systolic function by approximately 5% to 20% during AF, and the restoration of the sinus rhythm (SR) should have an opposite effect [4]. Unlike the short-term effects of AF on ventricular function, however, the long-term effects are more difficult to predict. Chronic AF, particularly if associated with inadequately controlled ventricular rate, may lead to progressive LV systolic dysfunction and dilatation [5]. On the other hand, the negative inotropic effect of chronically administered antiarrhythmic drugs may adversely effect LV systolic function following SR restoration [6].

Although AF is a relatively common significant arrhythmia, available data regarding the effect of SR restoration on LV function is based on only a few small observational studies. In particular, no studies have been performed to evaluate the long-term effects of rhythm versus rate control approach on LV function. Recently published AFFIRM and RACE trials did not confirm the superiority of SR restoration and the maintenance in terms of total mortality and the rate of thromboembolic complications [7, 8]. However, no data from these studies is available on the effect of rhythm versus rate control approach on LV systolic function.

The objective of this prospective multicenter study was to compare LV morphology and systolic function in patients with persistent AF randomized to rhythm versus rate control approach. This analysis was performed as a part of the HOT CAFE trial, the main findings of which were published previously [9].

Methods

Basic concepts

How To Treat Chronic Atrial Fibrillation (HOT CAFE) trial was an open prospective multicenter study performed in 6 cardiological centers (Katedra i Klinika Chorób Wewnętrznych i Kardiologii I Wydziału Lekarskiego Akademii Medycznej w Warszawie, Katedra i Klinika Chorób Wewnętrznych i Nadciśnienia Tętniczego I Wydziału Lekarskiego Akademii Medycznej w Warszawie, Oddział Kardiologiczny Szpitala Wojewódzkiego w Siedlcach, Oddział Wewnętrzny Szpitala w Milanówku, Oddział Kardiologiczny Szpitala Wojewódzkiego w Radomiu, Świętokrzyskie Centrum Kardiologiczne w Kielcach). The study was initiated in March 1997, randomization was continued until December 2000, and last follow-up visits were performed in December 2001.

The study was approved by the local ethics committees in participating centers. All patients gave written informed consent for the participation in the study.

Inclusion criteria

Patients aged 50–75 years were eligible for the study if they had persistent, symptomatic AF of ≤ 2 years of duration, with the removable or controllable cause of the arrhythmia and no contraindications to cardioversion and anticoagulation. The arrhythmia could be related to ischemic heart disease, hypertension, or hemodynamically insignificant valvular heart disease with the exception of mitral stenosis. Patients with lone AF could also be included.

Exclusion criteria

Exclusion criteria included the documented ineffectiveness/intolerance of or contraindications to antiarrhythmic drugs, the history of unsuccessful cardioversion of AF, thyreotoxicosis, pregnancy or lactation, myocardial infarction during the last month, coronary artery bypass grafting during the last 4 months, acute myocarditis, severe heart failure (New York Heart Association functional class IV), the history of transient ischemic attack with significant vascular pathology requiring invasive intervention, the history of hemorrhagic stroke, ischemic stroke during the last 3 months, vascular heart disease (with the exception of mitral stenosis) requiring surgical treatment, any mitral stenosis, severe uncontrolled hypertension (diastolic blood pressure > 115 mm Hg), hypotension (systolic blood pressure < 90 mm Hg), pulmonary hypertension (tricuspid gradient > 35 mm Hg), significantly increased left atrium (short-axis diameter > 60 mm), heart rate during AF below 90/min without rate-controlling drugs, bundle branch block or prolonged QT interval (QTc ≥ 0.45 s), significant hepatic, renal or central nervous system dysfunction, neoplasm, alcohol abuse, advanced chronic obstructive

pulmonary disease or other severe disease, contraindications to anticoagulation, lack of adequate cooperation and lack of written informed consent.

Randomization and methods

Patients entering the trial were randomly assigned to one or two therapeutic strategies. Randomization was performed in the coordinating center (I Katedra i Klinika Kardiologii Akademii Medycznej w Warszawie).

The diagnosis of AF was made upon the analysis of a standard 12-lead electrocardiogram (ECG). In addition, 24-hour ambulatory ECG monitoring was performed to confirm the chronic nature of AF and exclude advanced atrioventricular conduction abnormalities. Patients fulfilling the entry criteria were randomly assigned to one of the following therapeutic strategies:

— optimal ventricular rate control and anticoagulation while in AF;
— restoration and maintenance of SR.

In both groups, patients were managed according to the current clinical practice of treating persistent AF [3, 4]. Details of the study protocol have been previously described [9].

Echocardiographic studies

Transthoracic echocardiographic studies were performed using Sonos 2000 (Hewlett-Packard), Sequoia 256 (Acuson), and HDI 5000 (ATL) systems with 2.5 MHz transducer. Studies were performed at a baseline, at 2 months (in patients undergoing cardioversion usually 1 month after cardioversion) and at 12 months. During an echocardiographic study, ECG was recorded from the limb leads. Dimensions of cardiac chambers were evaluated in the parasternal long-axis view using M-mode. Measurements were performed according to American Society of Echocardiography conventions [10]. The following echocardiographic parameters were evaluated: LV end-diastolic short-axis dimension (LVEDD), LV end--systolic short-axis dimension (LVESD; only for the purpose of the calculation of fractional shortening), and LV fractional shortening (FS). All morphologic parameters were averaged from five measurements in subsequent cardiac cycles.

Statistical analysis

Results for each visit are expressed as mean values ± standard deviation (SD) for continuous variables and numbers (percentages) for categorical variables. A two-step analysis was used to compare changes in echocardiographic parameters in the two study groups between the baseline, 2 months, and 12 months. ANOVA for repeated measurements was used to determine between- and within-group differences. If such differences were noted, comparisons between visits in a given group and between the two groups for a particular visit were performed using Student *t* test. Comparisons between subsequent visits in a given group were adjusted for repeated measurements. To avoid errors related to repeated comparisons, Bonferroni correction was applied. $P < 0.05$ was considered statistically significant.

Results

Study group characteristics

The study group consisted of 205 patients (F/M 71/134; 34.6%/65.4%) aged 50–75 years (mean age 60.8 ± 11.2 years) with persistent AF lasting from 7 days to 2 years who were randomized to rate versus rhythm control. Clinical characteristics and echocardiographic parameters of LV morphology and function in the study groups are summarized in Table 1.

A twelve month follow-up was completed in 200 patients. Four patients (2 F, 2 M) died during the follow-up, including two patients (1 F, 1 M) randomized to the rhythm control strategy who suffered a fatal massive ischemic stroke with major neurological deficit, 1 female patient who died in a traffic accident during the 10th month of follow-up, and 1 male patient who died due to a neoplasm. One male patient withdrew the consent 6 months before the completion of the follow-up.

Group I — ventricular rate control and anticoagulation in patients with AF

One hundred and one randomized patients (F/M 38/63; mean age 61.4 ± 17.6 years), were assigned to the rate control approach. To control ventricular rate while in AF, 8 patients (7.9%) were given calcium antagonists (verapamil or diltiazem), 50 patients (49.5%) were given beta-blockers, 40 patients (39.6%) were given beta-blocker and digoxin, and 3 patients (3.0%) were given only digoxin. As anticoagulation, acenocoumarol was used in 75 patients (74.3%), acetylsalicylic acid in 20 patients (19.8%), and ticlopidine in 1 patient (1.0%). Five patients (4.9%) were given no anticoagulation due to the low risk of thrombombolic complications.

Group II — SR restoration and maintenance

Elective DC cardioversion was performed in 104 patients (F/M 33/71; mean age 60.4 ± 7.9 years) assigned to the rhythm control approach. Initial cardioversion restored SR in 56 patients (53.8%). In 48 patients with unsuccessful initial cardioversion,

Table 1. Clinical characteristics of the two study groups

Parameter	Group I	Group II
Age (years)	61.4 ± 17.6	60.4 ± 7.9
Gender:		
females	38 (37.6%)	33 (31.7%)
males	63 (62.4%)	71 (68.3%)
Atrial fibrillation duration:		
7 days to 1 month	17 (16.8%)	16 (15.4%)
1 month to 1 year	53 (52.4%)	73 (70.2%)
1 to 2 years	31 (30.8%)	15 (14.4%)
Mean atrial fibrillation duration (days)	243.2 ± 137.3	220.4 ± 148.6
History of paroxysmal atrial fibrillation	42 (41.6%)	37 (35.9%)
Etiology of atrial fibrillation:		
ischemic heart disease	38 (37.6%)	52 (50.0%)
history of myocardial infarction	7 (6.9%)	7 (6.7%)
coronary artery bypass grafting	0 (0.0%)	1 (1.0%)
Hypertension	60 (59.4%)	72 (69.2%)
Valvular heart disease	15 (14.8%)	16 (15.4%)
Lone atrial fibrillation	25 (24.8%)	18 (17.3%)
Diabetes	18 (17.8%)	15 (14.4%)
NYHA class:		
I	48 (47.5%)	30 (28.8%)
II	48 (47.5%)	59 (56.7%)
III	5 (5.0%)	15 (14.4%)
Left ventricular end-diastolic diameter [mm]	50.8 ± 5.9	52.2 ± 6.8
Fractional shortening (%)	32.8 ± 6.6	29.9 ± 6.9

There were no significant differences between groups in all tested parameters

amiodarone was added in the overall loading dose of 12.0 g to 16.0 g prior to another attempt of DC cardioversion. During amiodarone loading, SR returned in 10 patients (9.6%). The second DC cardioversion was performed in 38 patients, resulting in SR restoration in another 24 patients (23.1%). Overall, SR was restored in 90 patients (86.5%).

Subsequent DC cardioversions and the use of antiarrhythmic drugs allowed to maintain SR during 12 months in 42 patients following initial successful cardioversion and in 24 patients following successful cardioversion preceded by amiodarone treatment. Overall, SR was maintained at 12 months in 66 patients (73.3% of all patients in whom SR was restored) or 63.5% of all patients in Group II. Amiodarone to prevent arrhythmia recurrence was given at 12 months in 37 patients (56.0% of all patients in whom SR was restored).

Effect of SR restoration and maintenance on changes in selected echocardiographic parameters

The dynamics of changes in echocardiographic parameters in the two study groups during the 12-month follow-up is shown in Table 2.

Changes of LV end-diastolic dimension. Initial evaluation using ANOVA showed significant change in mean LVEDD during the follow-up in the overall study group (time effect $p < 0.0001$, group effect $p < 0.03$).

Subsequent within-group analysis showed borderline significant decrease in LVEDD between 2 and 12 months in Group I ($p<0.05$). Borderline significant increase in LVEDD at 2 months was found in Group II ($p < 0.05$). There were no significant between-group differences throughout the follow-up. The dynamics of changes in mean LVEDD in the two study groups during the 12-month follow-up is shown in Table 2 and Figure 1.

Changes in LV fractional shortening. The initial evaluation using ANOVA showed a significant change in mean FS during the follow-up in the overall study group (time effect $p < 0.0001$, interaction effect $p < 0.0001$).

The subsequent analysis revealed modest time-dependent increase in FS in the overall study group. Significant increase in FS at 2 and 12 months compared to the baseline was found in Group II ($p < 0.001$). However, the latter might have resulted from initially lower FS in Group II ($p < 0.005$).

Table 2. Dynamics of changes in echocardiographic parameters in the two study groups during the 12-month follow-up

Parameter		Follow-up			p		
		Baseline	2 months	12 months	Group effect	Time effect	Interaction effect
Left ventricular end-diastolic diameter [mm]	Group I Group II	50.8 ± 5.6 52.2 ± 6.8	50.9 ± 5.7 53.4 ± 5.5	50.0 ± 6.0 52.0 ± 7.4	0.03	0.0001	NS
Fractional shortening **(%)**	Group I Group II	32.8 ± 6.6 29.9 ± 6.9	32.8 ± 6.7 33.3 ± 8.2	35.6 ± 7.4 31.3 ± 7.3	NS	0.0001	0.001

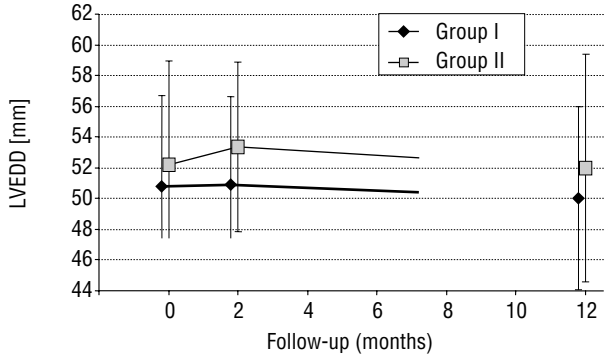

Figure 1. Changes in left ventricular end-diastolic diameter (LVEDD) in the two study groups during the 12-month follow-up.

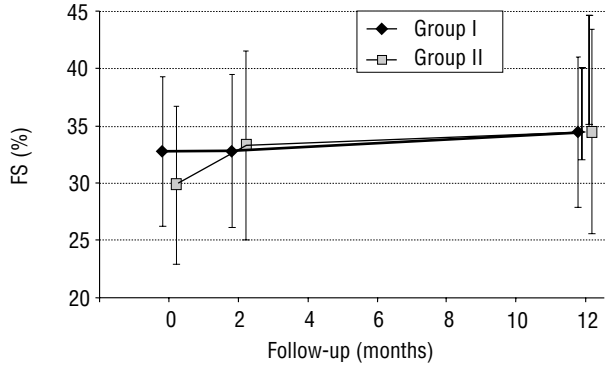

Figure 2. Changes in left ventricular fractional shortening (FS) in the two study groups during the 12-month follow-up.

There were no significant between-group differences in FS throughout the follow-up.

The dynamics of changes in mean FS in the two study groups during the 12-month follow-up is shown in Table 2 and Figure 2.

Discussion

Currently available knowledge regarding the effect of AF on LV morphology and function is based on pathophysiological considerations and the results of small short-term unrandomized observational studies. These studies compared patients with successful SR restoration and maintenance to patients in whom arrhythmia termination was not attempted or unsuccessful [11]. Most of these studies suggested benefits from SR restoration and maintenance. Such unrandomized observational studies are, however, subject to significant bias. First, actual treatment intention was not accounted for and the control groups included patients with both early and late failure of cardioversion. This mode of comparison might also lead to another bias, as patients in whom SR was maintained long-term might have less advanced underlying heart disease and thus show better parameters of LV systolic function during long-term follow-up. Finally, lack of randomization may also introduce significant bias.

To avoid these systematic errors, patients in our study were randomized to rate versus rhythm control, and the results were analyzed on an intention-to-treat basis, similarly to AFFIRM and RACE trials, currently constituting the knowledge base regarding the management of AF. However, the effect of both approaches on LV function was not a subject of direct assessment in these trials. A similar rate of heart failure regardless of the assignment to rate versus rhythm control may suggest that both approaches are associated with a similar effect on LV function.

The findings of our study confirm no significant positive effect of the rhythm control strategy on LV morphology and function. We found no significant difference in LV size between the two study groups. Modest initial difference in LV size seen in Group II at 2 months compared to the baseline seems to result from slower ventricular rate following SR restoration, leading to prolonged diastolic filling.

We also found no significant difference in LV systolic function between groups throughout one year follow-up. Of note, FS increased in the overall study group regardless of the assigned strategy, highlighting significant benefits resulting from the optimized management of persistent AF including adequate ventricular rate control and the treatment of coexisting conditions. The negative findings of our study may have been affected by the intention-to-treat analysis of data. Despite the surprisingly high effectiveness of attempts to restore and maintain SR, AF was seen at one year in 36% of patients in the rhythm control group.

It should be stressed that our study group seemed to be well representative for the average population of patients with AF. In particular, hypertension and coronary artery disease were common in our subjects, while the advanced heart failure was relatively rare (NYHA class III was seen in approximately 10% of patients). Of note, baseline systolic LF function in the overall study group was relatively preserved (mean FS 31%).

Our findings are apparently contradictory to the reports of the effects of SR restoration in patients with heart failure. In a study in more than 150 patients with heart failure, Okcun *et al.* reported significant improvement in LV ejection fraction (LVEF) at 1 year in patients randomized to the rhythm control group [12]. French authors studied 17 patients with dilated cardiomyopathy using radionuclide ventriculography and reported increased LVEF from 32% to 53% in 12 patients at 4 months following successful cardioversion. In contrast, LVEF remained unchanged in patients with unsuccessful attempts to cardiovert AF, and AF recurrence was associated with the impairment of LV systolic function [13]. Interesting data was recently reported by the Haissaguerre group. The ablation of AF within pulmonary veins was performed in 58 patients with symptomatic heart failure and reduced LVEF (35%). At 12 months, SR was maintained in 78% of patients and an absolute increase in LVEF by 21% was seen in these patients, both in subjects with tachyarrhythmia-induced cardiomyopathy and, albeit to a lesser extent, in patients with heart failure resulting from other underlying structural cardiac disease [14]. Atrioventricular node ablation to control ventricular rate by ventricular pacing may also have a positive effect on LV systolic function in some patients with impaired LV function [15].

However, our study group included only few patients with a significantly impaired LV function. The positive effect of SR restoration on LF function in patients of heart failure may be related to the presence of tachyarrhythmia-induced cardiomyopathy as the underlying or coexisting cause of heart failure. In addition, optimal LV filling achieved with atrial contraction and the lack of increased heart rate that is commonly seen in AF may be much more important in patients with impaired LV systolic function than in those with preserved LV systolic function at baseline. In the former, systolic function may be improved when decompensating factors are removed, while in the latter restoration of SR is of less importance and has no significant effect on LV size and systolic function.

Our findings lead to some interesting conclusions. It seems that active attempts to restore and maintain SR in patients with preserved systolic function have no effect not only on mortality and thromboembolic risk, but also on LV function. This may be yet another argument in favor of rate control approach in patients with recurrent AF. On the other hand, SR restoration may be particularly beneficial in patients with underlying impairment of LV function. These patients may prove difficult to maintain SR but the effect on LV function may contribute to improved prognosis. With unfavorable long-term effectiveness of drug treatment and promising results of non-drug therapy, more aggressive management including antiarrhythmic ablation should be considered in these patients.

Conclusions

In an unselected group of patients with persistent AF and largely preserved LV systolic function, rate control approach has no significant effect on LV size and systolic function compared to rhythm control approach.

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