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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The effect of strict rate control on B-type natriuretic peptide values and echocardiographic parameters in chronic atrial fibrillation

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Abstract

Background: There have been conflicting results about the role of strict rate control on cardiovascular outcomes in patients with chronic atrial fibrillation (AF). To date, large clinical studies have not shown a net clinical benefit derived from the current trend to specify the target ventricular rate according to the patient's own clinical and laboratory characteristics. Although the existing literature shows no superiority of strict rate control in clinical end points, it is difficult to assess the pure rate effect without commonly coexisting medication side effects which can also influence clinical end points.

Aim: To determine the effects of strict rate control in patients with chronic AF, regarding objective parameters such as echocardiographic data and B-type natriuretic peptide (BNP) values.

Methods: 38 patients with chronic AF for whom strict rate control had been planned were enrolled in the study. Patients' echocardiographic parameters, BNP values and 24 h Holter electrocardiography findings showing the average heart rate (HR), were studied at baseline and then monthly, until the end of the 3rd month. Patients' negative dromotropic therapy was adjusted to achieve a target resting HR of below 80 bpm. Laboratory and echocardiographic parameters at baseline and at the end of the study were compared in the whole study group. The whole study group was subclassified according to the average resting HRs achieved, (group 1 with strict rate control < 80 bpm; n = 25, and group 2 without strict rate control; n = 13).

Results: In group 1, the average HR declined from 101 ± 16.3 bpm to 77 ± 5.2 bpm. In group 2, the average HR was 96.6 ± 6.8 bpm at baseline and there was no significant change at the end of the study (94.2 ± 5.9 bpm). In group 1, there were significant decreases in BNP, left ventricular volumes, left atrial and right atrial areas at the end of the study. In group 2, BNP values were significantly higher at the end of the study despite similar ventricular and atrial dimensions according to the baseline. Diastolic functions were assessed roughly by septal E/e', but no significant change was observed in either group.

Conclusions: Strict rate control in patients with chronic AF yielded a significant decrease in BNP values as well as a reduction in volumes of cardiac chambers.

Key words: atrial fibrillation, heart rate, B-type natriuretic peptide, cardiac remodelling

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INTRODUCTION

There is little doubt that heart rate (HR) is a risk factor for cardiovascular mortality, independent of currently accepted risk factors [1]. HR control is a target of therapy in systolic heart failure, in ischaemic heart disease, and even in diastolic heart failure. In all of these situations, lowering resting HR below 70 bpm is associated with symptom relief and/or increased survival [2, 3]. On the other hand, the targets for HR in atrial fibrillation (AF) remain doubtful, despite the common coexistence of AF with structural heart diseases. This is partly due to a lack of sufficient data to define an optimal HR in AF and also due to the difficulties in lowering ventricular rates without any side effect of the used medicines. Current AF guidelines recommend a resting HR goal of < 110 bpm which is indeed a very high value respectively [4, 5]. Although the existing literature shows no superiority of strict rate control in clinical end points, it is difficult to assess the pure rate effect without commonly coexisting medication side effects which

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can also influence the clinical end points. In this study, we aimed to determine the effects of strict rate control in patients with chronic AF, regarding the objective parameters such as echocardiographic data and B-type natriuretic peptide (BNP) values.

METHODS

Study population

A total of 80 patients with chronic AF for whom strict rate control had been planned were screened for the study. Of these, 40 were enrolled in the study. Two patients were excluded after the first Holter electrocardiography (ECG) evaluation, as their heart rhythm was shown to be paroxysmal AF rather than permanent. Left ventricular (LV) systolic dysfunction, severe valvular heart disease, any systemic disease which could affect the HR, and basal HR below 80 bpm, were defined as the exclusion criteria. Mean age of the total study population (n = 38) was 69.6 ±12 years. 21 (55%) patients were male, 33 (86%) patients were hypertensive, and 18 (47%) patients were diabetic. A history of coronary artery disease was evident in five (13%) of the patients. The study population consisted of patients in New York Heart Association class 1 or 2; class 3 and class 4 patients were excluded from the study. Average resting HR of the whole population was 98 ± 14.8 bpm at baseline. At the end of the three month follow-up period, the population was subclassified according to the HR achieved, group 1 (n = 25) with strict rate control (resting HR < 80 bpm), and group 2 (n = 13) with lenient rate control (resting HR > 80 bpm).

Protocol

The study protocol was approved by the local ethical committee. After providing written informed consent, resting ECG, 24 h Holter ECG recording, transthoracic echocardiography and BNP evaluation were performed to obtain baseline measurements. Patients' medical therapy was adjusted according to this baseline evaluation targeting a resting HR < 80 bpm. For this purpose, negative dromotropic drugs were either up-titrated or added on according to the baseline status of the medications used. First line negative dromotropic therapy was beta-blockers or calcium channel blockers, selected according to the comorbidities of the patients. Digoxin was added as second line therapy after achieving the maximum tolerated dose of the first drug. Triple therapy including beta-blockers, calcium channel blockers and digoxin was used only in one patient in group 1, and in two patients in group 2. Major adverse events limiting the up-titration of the negative dromotropic therapy were hypotension, decrease in exercise capacity, and constipation. Other medical therapies including diuretics, renin–angiotensin system blockers, and other hypertensives were not altered by the monitoring physician during the entire follow-up. Patients were re-evaluated by resting ECG and Holter ECG monthly, to make the necessary drug adjustments for achieving the target HR. At the end of the 3rd month, patients' final assessments were performed including echocardiography and BNP measurement.

Measurements

The resting HR was measured by means of a 12-lead ECG after 2-3 min of rest in the supine position. Exercise HR was defined as the average HR during moderate exercise which was assessed through the recordings of the Holter ECG (Del Mar Reynolds Medical).

Blood samples for BNP levels were drawn in the morning, in fasting and supine patients. Plasma BNP level was determined immunoenzymatically using the AxSYM kit (Abbott). The reference range of plasma BNP levels determined using quantitative Abbott immunoenzymatic kits is 0.00–100.00 pg/mL.

Transthoracic echocardiography was performed using a HD11XE Philips echocardiography machine with a 2.5––3.5 MHz probe. All standard echocardiographic parameters were evaluated, with particular attention to LV volumes, atrial dimensions and diastolic Doppler parameters. All of the measures were made by the same trained investigator who was blind in respect of patient classification.

Statistical analysis

The SPSS statistical software (SPSS for Windows 15.0, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean ± standard deviation, and categorical variables were defined as percentages. Comparisons between the different data for each patient at different time points of assessment were performed with two-tailed paired Student's *t* test. Delta values for parameters were calculated in each group according to the difference between the final and baseline values. Comparisons of delta values in each group were performed by independent sample Student's *t* test. Categorical variables among two subgroups were compared by χ^2 test. Pearson correlation was used to evaluate the association between the parameters. Statistical significance was defined as $p < 0.05$.

RESULTS

Patients were followed up for three months. There were no thromboembolic complications during this follow-up period. At the end of three months of follow-up, 25 patients achieved the target resting HR (group 1). In this group, the resting HR decreased from 101 ± 16 bpm to 77 ± 5 bpm, and the exercise HR decreased from 125 ± 24 bpm to 97 ± 12 bpm. In the remaining 13 patients (group 2), the resting HR did not change significantly at the end of the study (96 ± 6 vs. 94 ± 5 bpm). However, the exercise HR decreased significantly from 123 ± 13 bpm to 110 ± 17 bpm. The main reason for such an ineffective rate control in group 2 was the side effects of the used drugs, limiting the necessary up-titration. The

baseline clinical and laboratory characteristics of the groups are outlined in Table 1. There was no significant difference between the baseline parameters of the groups, except for the higher BNP values in group 1 (392 ± 272 vs. 265 ± 14 pg/dL, p = 0.03).

The final changes in laboratory and echocardiographic parameters according to baseline values are summarised separately for both groups in Tables 2 and 3. In group 1, BNP values, LV volumes, right ventricular areas, and atrial areas decreased significantly at the end of the follow-up. However, Doppler parameters focusing on diastolic functions did not change significantly (Table 2). In group 2, there were no significant changes in any of the echocardiographic parameters, despite a surprising increase in BNP values according to the baseline levels (Table 3, Fig. 1).

Delta values for parameters were also assessed in each group calculating the difference between the final and baseline values. Comparison of these delta values showed significant differences between the groups in respect of BNP, resting HR, exercise HR, LV end diastolic volume, left atrial area and right atrial area (Table 4). In group 1, the delta values for the mentioned parameters were significantly higher than the delta values in group 2.

In group 1, the change in BNP values were found significantly correlated with the changes in resting HR (r = 0.51, p = 0.008), exercise HR (r = 0.61, p = 0.001) and left atrial area (r = 0.48, p = 0.015). It was obvious that the most powerful correlate of the BNP change was the change in exercise HR.

Table 1. Baseline clinical and demographic characteristics of the groups

	Group 1 (n = 25)	Group 2 (n = 13)	P
Age [years]	71.4 ± 14	66.4 ± 12	0.110
Male	12 (48%)	9 (69.2%)	0.183
Diabetes mellitus	12 (48%)	6 (46.2%)	0.593
Hypertension	20 (80%)	12 (92.3%)	0.106
Chronic kidney disease	1 (4%)	2 (15.2%)	0.265
Coronary artery disease	4 (16%)	1 (7.7%)	0.433
Cerebrovascular event	3 (12%)	1 (7.7%)	0.576
Smoking	5 (20%)	3 (23.1%)	0.568
Chronic obstructive pulmonary disease	8 (32%)	4 (30.8%)	0.619
Height [cm]	166.2	168.5	0.345
Weight [kg]	83.4	83.3	0.314
ACEI/ARB	23 (92%)	11(84%)	0.533
Loop diuretics	10 (40%)	5 (38%)	0.695
Aldosterone antagonist	8 (32%)	3 (23%)	0.515
GFR [mL/min]	66 ± 38	60 ± 30	0.150
B-type natriuretic peptide [pg/dL]	392 ± 272	265 ± 142	**0.01**

ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; GFR — glomerular filtration rate (Cockroft and Gault equation)

Table 2. Comparison of baseline and final parameters in Group 1

	Baseline value	Final value	P
B-type natriuretic peptide [pg/dL]	392 ± 272	249 ± 224	**< 0.001**
Resting heart rate [bpm]	101 ± 16.3	77 ± 5.2	**< 0.001**
Exercise [bpm]	125 ± 24	97 ± 12	**< 0.001**
LV ejection fraction [%]	56.8	56.9	0.714
LV ESV [mL]	59 ± 8.9	57.8 ± 9.4	**0.017**
LV EDV [mL]	119.7 ± 19.7	116 ± 18	**< 0.001**
RV EDA [cm^2]	18.8 ± 7	18.3 ± 6.3	0.205
Left atrial area [cm^2]	30.7 ± 7.4	29.8 ± 7.3	**0.004**
Right atrial area [cm^2]	23.4 ± 5.6	22.6 ± 5.4	**< 0.001**
E [cm/s]	130.1 ± 30	128.1 ± 31	0.200
Deceleration time [ms]	196.3 ± 50.1	202 ± 51.8	0.176
IVRT [ms]	63 ± 11.3	63 ± 10.6	0.974
PAB [mm Hg]	29.4 ± 5.8	29.2 ± 5.1	0.655
e' [cm/s]	12.1 ± 2.8	12.0 ± 3.0	0.879
E/e'	12 ± 4.2	11.8 ± 4.2	0.102

E — mitral filling Doppler velocity; e' — LV rapid filling phase tissue Doppler velocity; EDA — end diastolic area; EDV — end diastolic volume; ESV — end systolic volume; IVRT — isovolumetric relaxation time; LV — left ventricular; PAB — systolic pulmonary artery pressure; RV — right ventricular

Table 3. Comparison of baseline and final parameters in Group 2

	Baseline value	Final value	P
B-type natriuretic peptide [pg/dL]	265 ± 142.6	389 ± 191.5	**0.01**
Resting heart rate [bpm]	96.6 ± 6.8	94.2 ± 5.9	0.697
Exercise [bpm]	123.2 ± 13.7	110.8 ± 17.9	**0.05**
LF ejection fraction [%]	57.9 ± 3.6	57.8 ± 4.4	0.88
LV ESV [mL]	60.5 ± 7.2	60.0 ± 8.8	0.565
LV EDV [mL]	127 ± 13.1	127.3 ± 15.8	0.868
RV EDA [cm^2]	20.3 ± 5.5	20.6 ± 6.2	0.354
Left atrial area [cm^2]	31.4 ± 11.6	32 ± 12.5	0.094
Right atrial area [cm^2]	23.3 ± 4.5	24.1 ± 5.3	**0.034**
E [cm/s]	132.9 ± 14.2	130.2 ± 25.2	0.09
Deceleration time [ms]	216.5 ± 61	219.8 ± 51.7	0.181
IVRT [ms]	67.8 ± 14.2	66.8 ± 13.4	0.258
PAB [mm Hg]	30.6 ± 5.6	32.3 ± 6.6	0.180
e' [cm/s]	10.6 ± 1.4	10.5 ± 1.5	0.455
E/e'	12.7 ± 2.9	12.6 ± 2.7	0.600

Abbreviations as in Table 2

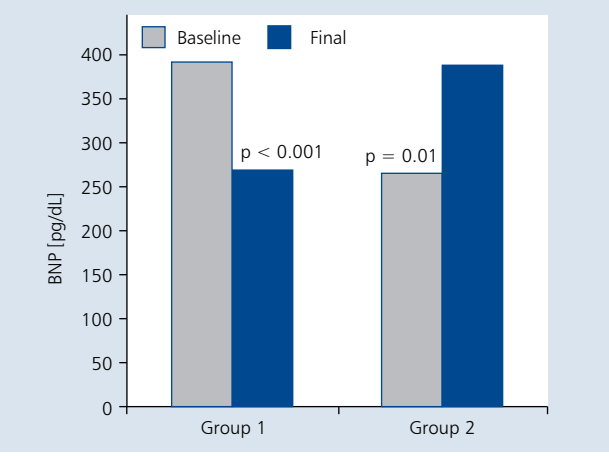

Figure 1. Baseline and final B-type natriuretic peptide (BNP) values in group 1 and group 2

DISCUSSION

In this study, the strict rate control yielded a reverse cardiac remodelling and prominent BNP lowering in a very short period of time. These results conflicted with the previous data in which strict rate control was not associated with a better clinical and echocardiographic outcome. The main reason for this controversy seems to be the higher HR in our lenient-control group. In the RACE II trial, which is the largest trial regarding this issue, the resting HR was 85 ± 14 bpm in the lenient-control group, which was substantially lower than in our study (94 ± 5 bpm) [6]. The small difference between the average HR of the two groups in the RACE II trial (10 bpm) may be a limiting factor for observing such a differential outcome. In RACE II, a resting HR below 110 bpm was stated as being low enough to prevent an increased number of hospitalisations for heart failure and also

Table 4. Comparison of delta values between groups

	Group 1	Group 2	P
Δ B-type natriuretic peptide	–143.8 ± 167.4	124.5 ± 145.6	**< 0.001**
Δ Resting heart rate	–23.9 ± 17.4	–1.15 ± 4.1	**< 0.001**
Δ Exercise heart rate	–27.7 ± 22.9	–12.4 ± 12.9	0.079
Δ LV ESV	–1.26 ± 2.45	–0.5 ± 3.1	0.429
Δ LV EDV	–3.7 ± 3.1	0.2 ± 5.2	**0.03**
Δ RV EDA	–0.43 ± 1.68	0.2 ± 1.0	0.104
Δ Left atrial area	–0.89 ± 1.4	0.76 ± 1.5	**0.01**
Δ Right atrial area	–0.8 ± 0.9	0.7 ± 1.1	**< 0.001**

Δ = final value–baseline value; EDA — end diastolic area; EDV — end diastolic volume; ESV — end systolic volume; LV — left ventricular; RV — right ventricular

to prevent a decrease in ejection fraction. One of the major concerns about the results of the RACE II trial is that not all patients achieved the HR target, especially not in the strict group. The inability to achieve the strict rate control target might have influenced the outcome in favour of lenient rate control. A recently published post-hoc analysis of the RACE II trial answered this question via analysing the failed strict rate control patients separately. Groenveld et al. [7] found that there was also no difference in cardiovascular outcome between successful strict, failed strict, and lenient, rate control in patients with permanent AF. In addition, quality of life was comparable between the groups at the end of the follow-up. However, in another study pooling the data of the AFFIRM and RACE trials, it was demonstrated that HR > 100 bpm was associated with a poor clinical outcome in AF patients [8]. Moreover, considering the small number of patients with HR above 90 bpm in all of these trials, we think that it is not so convenient to state the target HR as < 110 bpm in AF patients. As AF is mostly a consequence of underlying structural heart disease such as diastolic heart failure, systolic heart failure, and coronary artery disease, even a HR of 110 bpm is unfavourable for such disease states. The only exception is lone AF, although the ratio of lone AF was only 1.8% in the whole study population in RACE II [6].

One of the main reasons for recommending such a higher target HR in AF patients was the higher rates of adverse effects of drugs, syncope, and pacemaker implantation in strict rate groups. This was especially prominent in the AFFIRM study in which the rate of pacemaker implantation was substantially high; 7.3% in 3.5 years of follow-up [9]. Obviously, the more negative dromotropic drugs are given to obtain a certain HR, the greater the risk of producing symptomatic bradycardia. Although a strict rate control may have been beneficial in some patients, this may also have come at the price of iatrogenic bradycardia and excess implantation of pacemakers in others. Additionally, high dose beta-blocker usage, which usually causes fatigue, reduced exercise capacity, and poorer social functioning, is another factor covering up the potential clinical benefits of strict rate control. The objective of this study in focusing on the echocardiographic and laboratory parameters was to bypass such drug related adverse effects, thus presenting the net effect of strict rate control.

AF is a process which is associated with electrical, neurohormonal and structural remodelling of the heart over the long term. This remodelling causes atrial enlargement, ventricular enlargement, reduced systolic function, and also ventricular diastolic dysfunction. Although diastolic dysfunction was known as a cause rather than a consequence of AF, today there also appears to be too much evidence of interplay between AF, heart failure and diastolic dysfunction for one to cause the other with causal reciprocation [10]. AF impairs cardiac function via several mechanisms such as the loss of atrioventricular synchrony and atrial contraction, the reduction of diastolic filling, and the induction of a tachycardia-induced cardiomyopathy [11].

Increased BNP levels in AF are actually a consequence of all of these processes. Several studies have shown that BNP levels increase in patients with AF. In summary, these studies showed that BNP was useful in predicting the success of cardioversion, in establishing the underlying diastolic dysfunction, and also in differentiating the type of AF, i.e. whether it is paroxysmal or permanent [12, 13].

However, the relationship between the HR and BNP values has not been evaluated so far in AF patients. This study is the first demonstrating the effect of strict rate control on BNP values. Strict rate control yielded a prominent decrease in BNP values in our study. This decrease was thought to be a consequence of the established negative remodelling of the heart and also of a probable improvement in diastolic functions. Although not supported by the Doppler parameters, we think that strict rate control improved the diastolic functions mainly via lengthening diastolic filling time. This increase in diastolic filling period causes improvements in diastolic filling and left atrial emptying, resulting in a decrease in the stretch of the left atrium and pulmonary veins. Considering the limited efficacy of the echocardiographic parameters in the detection of diastolic dysfunction in AF, we think that it is not possible to exclude such a diastolic improvement due to lack of Doppler findings, especially when regarding the limited size of our study population.

The limited role of echocardiography in the diagnosis of diastolic dysfunction in AF was also proven in a prior study in which haemodynamic evaluation showed high LV filling pressures and high nadir of the left atrial Y descent in lone AF patients in the absence of Doppler criteria for diastolic dysfunction [14]. We also think that the prominent decreases in BNP values were out of proportion with the minor changes observed in cardiac chamber sizes. As mentioned previously, high BNP levels in patients with AF have been shown to be associated with underlying diastolic dysfunction. Considering these data, the prominent decrease in BNP in our study is thought to be a consequence of an improvement in diastolic functions. The effect of HR in diastolic functions has become a growing focus of interest even in patients with sinus rhythm. Some recent studies have shown that ivabradine therapy is associated with an improvement in diastolic functions as well [15]. We think that the contribution of a controlled HR to the improvement of diastolic functions is greater in AF, as the diastolic filling is completely passive and time dependent.

Another important finding of this study was the powerful correlation between BNP reduction and exercise HR reduction. Although the changes in resting HR and left atrial area were also significantly correlated with BNP change, the most powerful correlate of BNP was the change in exercise HR. This is mostly due to the limited efficacy of resting HR in the evaluation of rate control. Many patients with AF can

have optimal resting HR despite high HR, even with minimal exercise. In our opinion, it is not convenient to rely on resting HR solely for the evaluation of effective rate control. This issue is actually one of the major limitations of the RACE II trial, in which rate control was evaluated only by resting HR [6].

Limitations of the study

The small population of the study group undoubtedly limits the study. Although the results achieved statistical significance, they must be considered carefully and require further investigation and confirmation. Moreover, the relatively short follow-up period could also be a limiting factor for observing greater changes in cardiac remodelling. Use of two-dimensional echocardiography for volumetric analysis is another limitation of the study. LV diastolic function was assessed noninvasively by Doppler echocardiography, and although this method is widely applied, it is not a gold standard, especially in patients with AF. Resting HR was defined as the HR on ECG after 2–3 min of rest. An argument could arise whether the average HR on 24 h Holter ECG recordings should be preferred for this description. Although this data was already available, we preferred to use the resting ECG values in order to follow the guideline description of resting HR in AF.

CONCLUSIONS

This study presented a net benefit of strict rate control in patients with AF, in cardiac remodelling and diastolic functioning. This benefit was also confirmed by the lowering of BNP values in the strict control group. The established net benefit is thought to be particularly due to a greater difference of HR between the groups compared to the previous trials. Considering these results and the previous data, we think that the target HR in chronic AF patients must not be as low as in the strict rate control definition, but equally must not be as high as the actual recommendation. We think more data is needed to establish a more reasonable target HR in chronic AF.

Conflict of interest: *none declared*

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Wpływ ścisłej kontroli rytmu serca na stężenie peptydu natriuretycznego typu B i parametry echokardiograficzne w przewlekłym migotaniu przedsionków

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Streszczenie

Wstęp: Wyniki badań dotyczących wpływu ścisłej kontroli rytmu serca na sercowo-naczyniowe punkty końcowe u chorych z przewlekłym migotaniem przedsionków (AF) są sprzeczne. W dużych badaniach klinicznych nie wykazano dotychczas korzyści klinicznych netto, dlatego obecnie dąży się do określenia docelowej częstotliwości rytmu komorowego w zależności od parametrów klinicznych i laboratoryjnych danego pacjenta. Wprawdzie w dostępnych publikacjach nie wykazano dodatkowych korzyści wynikających ze ścisłej kontroli częstotliwości rytmu serca w odniesieniu do klinicznych punktów końcowych, ale należy pamiętać, że trudno ocenić czysty efekt ścisłej kontroli częstotliwości rytmu serca bez występujących często działań niepożądanych stosowanych jednocześnie leków, które również wpływają na punkty końcowe.

Cel: Celem niniejszego badania było ustalenie wpływu ścisłej kontroli rytmu serca u chorych z przewlekłym AF na obiektywne parametry, takie jak dane echokardiograficzne i stężenie peptydu natriuretycznego typu B (BNP).

Metody: Do badania włączono 38 chorych z przewlekłym AF, u których planowano utrzymywanie ścisłej kontroli rytmu serca. Na początku badania, a następie co miesiąc u każdego pacjenta analizowano parametry echokardiograficzne, stężenie BNP i zapis całodobowego monitorowania elektrokardiograficznego pokazujący średnią częstotliwość rytmu serca. U pacjentów odpowiednio dobrano dawkowanie leków o ujemnym działaniu dromotropowym, aby uzyskać docelową spoczynkową częstotliwość rytmu serca poniżej 80 uderzeń/min. W całej badanej grupie porównano parametry laboratoryjne i echokardiograficzne uzyskane wyjściowo i na końcu badania. Wszystkich uczestników badania podzielono na grupy w zależności od osiągniętej średniej spoczynkowej częstotliwości rytmu serca (grupa 1 ze ścisłą kontrolą rytmu serca < 80 uderzeń/min; $n = 25$ i grupa 2, w której nie osiągnięto ścisłej kontroli rytmu, $n = 13$).

Wyniki: W grupie 1 średnia częstotliwość rytmu serca zmniejszyła się ze $101 \pm 16{,}3$ uderzeń/min do $77 \pm 5{,}2$ uderzeń/min, a w grupie 2 parametr ten wynosił na początku badania $96{,}6 \pm 6{,}8$ uderzeń/min i nie zmienił się istotnie do zakończenia badania ($94{,}2 \pm 5{,}9$ uderzeń/min). W grupie 1 stwierdzono istotne zmniejszenie stężenia BNP, objętości lewokomorowych oraz powierzchni lewego przedsionka i lewej komory w okresie obserwacji. W grupie 2 stężenie BNP było istotnie wyższe w momencie zakończenia badania, mimo że wymiary komór i przedsionków nie różniły się od wartości wyjściowych. Czynność rozkurczową oceniono orientacyjnie na podstawie wartości współczynnika E/e', jednak w żadnej grupie nie stwierdzono istotnych zmian.

Wnioski: Ścisła kontrola rytmu serca u chorych z przewlekłym AF powoduje istotną redukcję stężenia BNP oraz zmniejszenie objętości komór serca.

Słowa kluczowe: migotanie przedsionków, częstotliwość rytmu serca, peptyd natriuretyczny typu B, przebudowa serca

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