

High concentrations of B-type natriuretic peptide and left ventricular diastolic dysfunction in patients with paroxysmal/persistent atrial fibrillation as possible markers of conversion into permanent form of arrhythmia: 1-year prospective evaluation

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Abstract

Background: Atrial fibrillation (AF) may cause electrical and structural atrial remodelling, leading to progression from paroxysmal to permanent form of arrhythmia. Predictors of such a transition have not yet been well established.

Aim: To assess the role of B-type natriuretic peptide (BNP) and left ventricular (LV) diastolic impairment in prediction of progression from paroxysmal/persistent AF to permanent AF.

Methods: The study group consisted of 154 patients (84 males, mean age 65.8 ± 10 years) with paroxysmal (51%) or persistent (49%) AF and normal LV systolic function. All patients had BNP level and echocardiographic parameters of diastolic LV dysfunction measured at baseline and after one-year follow up.

Results: After one-year follow-up, 15 (9.5%) patients developed permanent AF. These patients had significantly higher baseline and one-year BNP values than the remaining patients (96.0 vs 41 pg/mL, $p < 0.005$, and 151.1 vs 32.5 pg/mL, $p < 0.0001$, respectively). Also echocardiographic indices of LV diastolic dysfunction were abnormal in patients who developed permanent AF. Stepwise logistic regression analysis revealed that baseline BNP level had independent prognostic value in predicting permanent AF development (OR 1.06, CI 1.01–1.12, $p < 0.0162$). The area under ROC curve was 0.787.

Conclusions: Patient with normal systolic LV function and paroxysmal or persistent AF are likely to progress into permanent AF when they have increased BNP levels and echocardiographic signs of LV diastolic dysfunction.

Key words: atrial fibrillation, BNP, diastolic dysfunction

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INTRODUCTION

Type B natriuretic peptide (BNP) is released by cardiomyocytes in response to cardiac wall stress, volume overload and pressure increase [1]. It has vasodilatative properties, increases diuresis, and as a consequence, lowers blood pressure and decreases ventricular preload. The BNP inhibits sympathetic activity, rennin–angiotensin–aldosterone system and al-

dosterone itself. It has anti-proliferative and anti-fibrotic properties in the cardiac muscle [2].

To exclude the diagnosis of congestive heart failure (CHF), the cut-off BNP concentration was set at 75 pg/mL or less and to confirm the diagnosis, the cut-off was 500 pg/mL or more (sensitivity 88%, specificity 99%). The BNP concentration increase can be seen in many disorders that lead to atrial

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overload [3]. In patients with atrial fibrillation (AF), increased BNP level was reported in patients with persistent and permanent form of arrhythmia. Concentrations as little as 20 pg/mL or more are related to increased risk of CHF and AF occurrence [4]. Atrial fibrillation can cause electrical, neurohormonal and structural remodelling of the heart and in a longer period of time leads to its insufficiency.

The aim of the study was to assess the prognostic value of BNP concentrations and left ventricular (LV) diastolic function indices in prediction of conversion of paroxysmal/persistent AF into permanent AF in patients with preserved LV systolic function.

METHODS

Study group

Patients with paroxysmal/persistent recurrent AF and preserved systolic function were included. Patients with a history of CHF, valvular disease or cardiomyopathies were excluded. A prospective study was carried out between January 2005 and September 2008 and included 154 patients (84 [54.5%] males), aged 65.8 ± 9.6 years. Mean duration of arrhythmia was 4 years, quartile 1 (Q1) — 2 years, quartile 3 (Q3) — 7 years. Patients were not on antiarrhythmic drugs due to intolerance or lack of effect in terms of AF recurrence. All the patients (100%) received a beta-adrenergic agent (bisoprolol, metoprolol or propranolol) for prevention of AF recurrence and for rhythm control. Other drugs included: angiotensin-converting enzyme inhibitors: 70%, spironolactone: 59%, vitamin K antagonists: 60%, acetylsalicylic acid: 39%, statins: 58%.

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Study protocol

During the first visit, after informed consent and patient history were obtained based on an uniform questionnaire, ECG and echocardiography were carried out and blood samples were taken for BNP measurement. All the tests were repeated after 1 year. Standard 2D and Doppler echocardiography was performed. Triple measurement of the studied parameters was carried out in classical views on SONOS 5000 (Philips Medical Systems, Andover, Mass, USA). Left atrial measurements were taken in parasternal long axis and apical 4-chamber views (4CH). Ejection fraction was measured by the Simpson method. Diastolic function was measured by mitral inflow indices: early inflow velocity (E), late inflow velocity (A), E:A ratio and E wave deceleration time. Tissue Doppler indices were measured: early mitral annular velocity E' and E:E' ratio. The BNP was measured by radioimmuno-metric assay, (Roche Diagnostics, Mannheim, Germany), at baseline and at 12-months.

Statistical analysis

Statistical analyses were carried out by SAS 9.2 statistical package. Results are presented as mean values \pm standard deviation. Qualitative variables were assessed by χ^2 Pearson test or Fisher exact test and are presented as numbers and percentages in groups. For continuous variables demonstrating normal distribution, Student t test was used. For continuous variables demonstrating other types of distribution (BNP), non-parametric Mann-Whitney test was used. Results are presented as medians and upper and lower quartiles. Normality of data distribution was verified by Shapiro-Wilk test. A p value < 0.05 was considered significant.

RESULTS

Out of the 154 patients, 79 (51%) had paroxysmal AF, and 75 (49%) had recurrent persistent AF. In the persistent AF group men were the majority (69% vs 41%, $p = 0.0003$), electrical cardioversion was more frequently performed (49% vs 1.3%, $p < 0.0001$), more patients were hypertensive (83 vs 67%, $p = 0.0263$) and metabolic syndrome was more frequent with borderline statistical significance (51 vs 35%, $p = 0.0564$) than in patients with paroxysmal AF.

After 1 year follow-up, 15 (9.6%) patients, in whom persistent AF was previously diagnosed (100%), developed permanent AF (permanent AF group). Arrhythmia was well tolerated and pharmacological or electrical cardioversion was unsuccessful. Demographic and echocardiographic characteristics of the studied groups are presented in Tables 1 and 2.

At baseline, treatment of patients from the permanent AF group did not differ from the treatment of remaining patients. Pacemaker implantation and echocardiographic indices of diastolic dysfunction were more frequent in this group.

During 1-year follow-up, permanent pacemaker was implanted in 15 (9.7%) patients due to tachycardia-bradycardia syndrome: in 11 (7.8%) of patients with persistent sinus rhythm and in 4 (26.7%) of patients who developed permanent AF ($p = 0.04$).

In the permanent AF group, significantly higher BNP values were observed as compared with the remaining patients: 96.0 vs 41 pg/mL, $p < 0.005$ at baseline, and 151.1 vs 32.5 pg/mL, $p < 0.0001$ at 12 months (Fig. 1). No differences in BNP concentration were observed between hypertensive and non-hypertensive patients (Table 3).

The stepwise progressive logistic regression analysis revealed that out of all the studied variables, only BNP concentration and cardiac pacing had independent prognostic value for progression to permanent AF [odds ratios (OR) and confidence intervals (CI) are presented]: 1.06 (1.01–1.12, $p = 0.0162$) and 4.3 (1.0–16.3, $p = 0.0362$), respectively.

It was found that BNP concentration played a major role, with area under receiver-operator characteristic (ROC) curve (AUC) of 0.787. Pacing was a less important factor in the multifactorial analysis, as shown by AUC that increased only slight-

Table 1. Comparison of baseline demographic and clinical characteristics of the studied groups

	Permanent AF group n = 15	Non-permanent AF group n = 139	P
Age [years]	69.4 ± 9.8	65.5 ± 9.6	NS
Body mass index [kg/m ²]	27.0 ± 4.2	27.4 ± 3.5	NS
Sex: males	9 (60.0%)	77 (54.6%)	NS
Duration of arrhythmia [years]	4.5 (3–11)	4 (2.0–7.0)	NS
Cardiac pacemaker at 1 year	4 (26.7%)	11 (7.8%)	0.04
Radiofrequency ablation	0 (0%)	6 (4.3%)	NS
Electrical cardioversion	4 (26.7%)	34 (24.4%)	NS
Hypertension	14 (93.3%)	103 (73.0%)	NS
Stroke	2 (13.3%)	16 (11.4%)	NS
Coronary artery disease	5 (33.3%)	37 (26.4%)	NS
Type 2 diabetes	1 (6.7%)	15 (10.6%)	NS
Hyperlipidaemia	9 (60.0%)	71 (50.4%)	NS
Metabolic syndrome	8 (53.3%)	58 (41.1%)	NS
Thyroid disease	3 (20.0%)	28 (19.9%)	NS
Benign prostatic hyperplasia	3 (33.3%)	18 (23.4%)	NS
Hormonal replacement therapy	1 (6.7%)	15 (23.4%)	NS

tly, i.e. to 0.794. The sensitivity of such a model, however, characterised by accuracy of 91%, despite satisfactory C statistics (AUC = 0.794), was unacceptably low at the level of 7%, while specificity was as high as 99.3% (Fig. 2). Such result was probably due to the fact that in some of the patients who did not develop permanent AF, BNP concentrations were high because of concomitant risk factors and other disorders, despite the absence of CHF diagnosis.

Mean transverse atrial dimensions did not differ between the study groups (Table 2). It was demonstrated that E wave velocity was significantly higher and A wave velocity lower in subjects who developed permanent AF compared to the remaining patients, in whom recurrent forms of AF continued. Also the E:A ratio was significantly higher in permanent AF group. Values of the E:E' ratio higher than 15 were observed in 33% of patients in whom permanent AF developed (mean value 12.4 ± 4.8) and only in 11% of patients who did not develop permanent arrhythmia (mean value 10.1 ± 4.1); p < 0.05 (Table 2).

DISCUSSION

The BNP is the basic marker of CHF, but the concentrations of the peptide can be elevated in other disorders, including AF. Atrial fibrillation can be the cause as well as the consequence of CHF. In a study of 489 patients with CHF, including 16% of patients with AF, NT-pro-BNP concentrations were twice as high in AF patients as compared to those in sinus rhythm (3883 vs 1653 pg/mL). The NT-proBNP concentra-

tion was the most powerful, independent risk factor for mortality in this patient group [5].

Asymptomatic patients with AF and without CHF diagnosis have higher BNP levels than patients with sinus rhythm. However, initially, the importance of BNP level in AF patients was not appreciated. Conversely, the role of higher n-ANP concentrations was emphasised. In a series of studies from several centres, BNP was measured in different age-groups during arrhythmia and after conversion to sinus rhythm. It was demonstrated that BNP level was a predictor of effective AF cardioversion and subsequent maintenance of sinus rhythm.

In one of the studies, including 20 patients, mean BNP concentration was significantly higher prior to cardioversion as compared to 30 minutes after cardioversion: 197 ± 132 pg/mL vs 164 ± 143 pg/mL, p = 0.02. In patients in whom AF recurred within two weeks from cardioversion, BNP concentration was 293 ± 106 pg/mL, and in those in whom sinus rhythm was maintained, lower concentrations were found: 163 ± 122 pg/mL, p = 0.02 [6]. The same was demonstrated for CHF patients with comorbidities such as hypertension or coronary artery disease [1, 7–10]. Mean BNP concentrations after cardioversion in patients with paroxysmal AF were 28 pg/mL (n = 24) and in patients with persistent AF 41 pg/mL (n = 36) [9].

The role of diastolic heart failure has been increasingly recognised. In one of the studies it was demonstrated that the decrease of BNP level after conversion to sinus rhythm was greater in patients with diastolic heart failure (by 46%,

Table 2. Baseline echocardiographic parameters

	Permanent AF group n = 15	Non-permanent AF group n = 139	P
LVEDD [cm]	5.0 ± 0.6	5.0 ± 0.5	NS
LVESD [cm]	3.0 ± 0.6	3.1 ± 0.4	NS
IVS [cm]	1.2 ± 0.2	1.2 ± 0.1	NS
PWDD [cm]	1.0 ± 0.1	1.0 ± 0.1	NS
LVEDV [mL]	118 ± 31	118 ± 33	NS
LVESV [mL]	37.2 ± 18.5	40.2 ± 12.1	NS
RVDD [cm]	2.3 ± 0.6	2.4 ± 0.3	NS
Aorta [cm]	3.5 ± 0.4	3.6 ± 0.3	NS
EF [%]	69 ± 11	66 ± 6	NS
SF [%]	39.7 ± 9.2	36.3 ± 4.7	NS
SV [mL]	81.3 ± 23.9	77.6 ± 25.8	NS
LA length [cm]	5.3 ± 0.7	5.4 ± 0.7	NS
LA width [cm]	4.2 ± 0.5	4.3 ± 0.4	NS
LA area [cm ²]	19.3 ± 4.3	21.0 ± 4.1	NS
RA length [cm]	4.8 ± 0.7	5.0 ± 0.5	NS
RA width [cm]	3.7 ± 0.7	3.7 ± 0.6	NS
RA area [cm ²]	15.9 ± 4.6	17.0 ± 2.7	NS
E [m/s]	87 ± 18	72 ± 17	0.0269
A [m/s]	53 ± 22	69 ± 20	0.0523
E/A	1.7 ± 0.5	1.1 ± 0.4	< 0.001
E/E' > 15 [%]	33	11	< 0.05
DT [ms]	238 ± 100	234 ± 52	NS
IVRT [ms]	92 ± 17	110 ± 22	NS
Time A [ms]	138 ± 27	149 ± 26	NS
Tei LV index	0.48 ± 0.06	0.57 ± 0.17	NS

PAF — permanent atrial fibrillation; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; IVS — interventricular septum; PWDD — posterior wall diastolic diameter; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; RVDD — right ventricular diastolic diameter; LA — left atrial dimension (M-mode); EF — ejection fraction; SF — shortening fraction; SV — stroke volume; LA 2d length — left atrial long axis; LA 2d width — left atrial short axis; LA area — left atrial area; RA 2d long — right atrial long axis; RA 2d width — right atrial short axis; RA area — right atrial area; E — maximal velocity of early mitral flow; A — maximal flow velocity through mitral valve during atrial systole; DT — deceleration time; IVRT — isovolumetric relaxation time; E' — early mitral annulus diastolic velocity; A' — velocity of mitral annulus after atrial systole, Time A — time of mitral flow, Tei LV index — Tei left ventricular index

$p < 0.001$), whereas in patients with preserved diastolic function the decrease was not significant [11].

Higher BNP levels in patients with AF and diastolic LV dysfunction were also reported by other investigators. The BNP was a more sensitive and more specific marker in this patient group than ANP [12]. In our study, patients who developed permanent AF, demonstrated first stage diastolic dysfunction, what can be explained by greater risk of arrhythmia conversion to its permanent form within a short period of time, and by higher BNP levels.

The role of permanent cardiac pacing in the development of AF is also widely recognised. In our study, patients with sinus rhythm and without indications for cardiac pacing were included. After 1 year, cardiac pacemaker was implan-

ted in 15 (9.7%) patients, more frequently in patients from permanent AF group ($p = 0.04$). It can be inferred from CTOPP and MOST studies, as well as from meta-analyses, that right ventricular apical pacing increases the risk of persistent and permanent arrhythmia due to systolic ventricular dyssynchrony [13–15]. This in turn causes progression of electrical and structural remodelling of the atria and the ventricles, decreases refraction dispersion in the atria and impairs suppression of ectopic foci capable of AF initiation.

In our study, pacemaker implantation was a consequence of changes in the conduction system and taking into account the relatively short observation period (1 year), its impact on the course of arrhythmia was probably not clinically significant, despite the observed statistical trend.

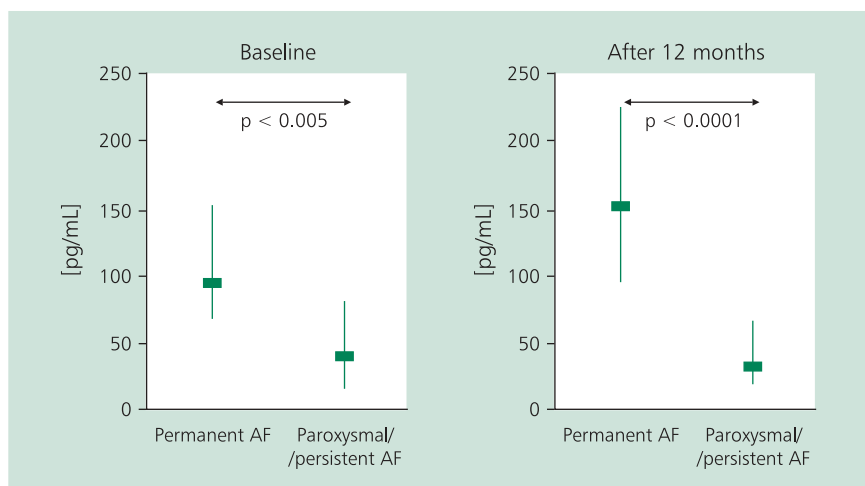


Figure 1. Comparison of BNP concentrations in patients who developed and who did not develop permanent atrial fibrillation (AF) at baseline and at one-year follow-up

Table 3. Comparison of BNP concentrations at baseline and at one year in hypertensive and non-hypertensive patients in both AF subgroups and in the entire study group

	No hypertension (27%) BNP concentrations [pg/mL]	Hypertension (73%) BNP concentrations [pg/mL]	P
Entire AF group			
Baseline	36.0 [14.0; 68.0]	44.5 [24.5; 91.0]	NS
At 1 year	36.0 [25.0; 53.0]	31.0 [17.0; 81.0]	NS
	NS	0.0067	
Paroxysmal/persistent AF			
Baseline	36.0 [18.0; 53.0]	40.0 [23.0; 67.0]	NS
At 1 year	33.5 [25.0; 46.0]	27.0 [17.0; 70.0]	NS
	NS	NS	
Permanent AF			
Baseline	37.0 [14.0; 80.0]	62.5 [28.0; 138.0]	NS
At 1 year	43.5 [10.5; 71.5]	42.0 [22.0; 147.0]	NS
	0.0100	0.0034	

AF — atrial fibrillation; BNP — B-type natriuretic peptide

Diastolic LV dysfunction is the cause of 30–50% of CHF cases. It can be assessed in patients with sinus rhythm as well as in patients with AF [16]. In one of the studies, in 28 patients with idiopathic AF, without structural heart disease in transthoracic and transoesophageal echocardiography, haemodynamic study revealed significantly elevated LV diastolic pressures as compared to controls ($n = 14$) [17].

It has been estimated that AF episodes occur in 25–30% of patients with diastolic CHF [18]. Diastolic LV dysfunction leads to higher filling pressures and to atrial remodelling, thus increasing the risk of AF, mainly by stimulating the stretch-sensitive ion channels. In a retrospective analysis Tsang et al. [19] de-

monstrated that diastolic dysfunction was an independent predictor of AF occurrence at 4 years. Hazard ratio (HR) of AF was directly related to diastolic dysfunction severity: relaxation disturbances: HR = 3.33; pseudonormalisation: HR = 4.84; restrictive physiology: HR = 5.26 [19]. In our study, conversion of AF to its permanent form occurred in a comparable proportion of patients, but patients in our group were younger (65.8 vs 75 years).

Other studies demonstrated a correlation between diastolic LV dysfunction (as assessed by traditional mitral inflow indices) and elevated ANP and BNP concentrations in patients with AF. Co-existence of these findings was related to

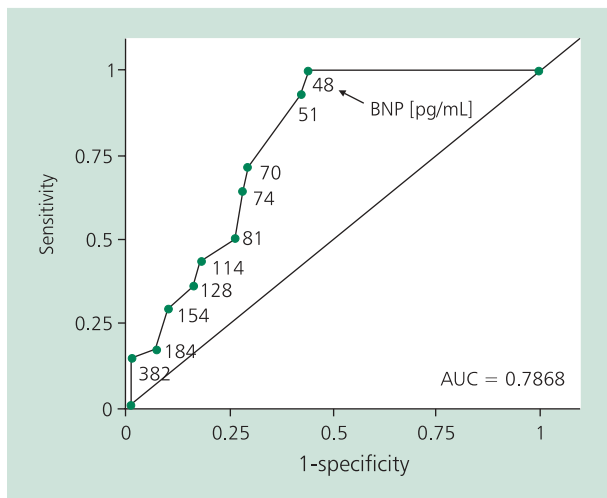


Figure 2. Receiver-operator characteristic (ROC) curve for different BNP cut-off values discriminating between patients who developed and who did not develop permanent atrial fibrillation

more frequent AF recurrence after ablation procedure [20]. It was also shown that improvement of LV haemodynamical status, as measured by ANP and BNP concentration decrease, was greater in patients with diastolic dysfunction [11]. In view of current guidelines concerning the diagnosis of CHF in patients with preserved LV systolic function, increased natriuretic peptide concentration itself is sufficient for the diagnosis of diastolic LV dysfunction in patients with AF [21–23].

In a study of comparable size, including 150 patients with AF, NT-proBNP concentrations were higher than in the controls (166 vs 133 fmol/mL, $p = 0.0003$). Interestingly, however, there were no differences in NT-proANP levels [24]. In a non-homogenous group of 1321 patients with serious comorbidities (LV and RV dysfunction, valvular heart disease, significant LV hypertrophy), BNP levels were significantly higher in patients with AF. The authors emphasize the need of setting the cut-off point for BNP concentrations, stratified by age, sex, renal status, body mass index, clinical status and other variables, especially in patients with structural heart disease [25].

Observational studies showed that as more advanced forms of AF develop, BNP concentrations increase progressively, indicating significant haemodynamic alterations in cardiac chambers. Despite wider implementation of BNP and NT-proBNP concentration measurements in the management of CHF patients and decreasing cost of these assays, the assessment of BNP in AF patients still cannot be considered a routine procedure. It is possible that natriuretic peptide measurement and LV function assessment can help in further strategy selection (rhythm or rate control). Most studies focu-

sed on BNP concentrations in AF patients in relation to arrhythmia recurrence. In our study, we tried to evaluate the potential relevance of BNP measurements for prediction of arrhythmia conversion to the permanent form, resistant to cardioversion attempts.

Is intensive pharmacological treatment (with rennin–angiotensin–aldosterone system inhibitors, beta-adrenolytics, diuretics), improving cardiac haemodynamics, in patients with AF and diastolic LV dysfunction, capable of deferring or decreasing the risk of conversion to the permanent form of arrhythmia? Further clinical studies are needed to answer this question.

CONCLUSIONS

In patients with recurrent paroxysmal/persistent AF, increased BNP concentrations and symptoms of diastolic LV dysfunction can be the risk factors of AF conversion into permanent form within a short period of time.

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Podwyższone stężenie peptydu natriuretycznego typu B i dysfunkcja rozkurczowa lewej komory u chorych z napadowym/przetrwałym migotaniem przedsionków jako czynniki ryzyka przejścia w utrwaloną formę arytmii: prospektywna obserwacja 1-rocza

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Streszczenie

Wstęp: Migotanie przedsionków (AF) może powodować elektryczną i strukturalną przebudowę serca. Wzrost osoczowego stężenia peptydu natriuretycznego typu B (BNP) obserwuje się m.in. w stanach prowadzących do przeciążenia przedsionków.

Cel: Celem pracy była ocena stężenia osoczowego BNP w prospektywnej obserwacji u pacjentów z różnymi postaciami AF, z prawidłową funkcją skurczową lewej komory.

Metody: Prospektywne badanie, przeprowadzone w okresie od stycznia 2005 do września 2008 roku, objęło grupę 154 pacjentów, w tym 84 (54,5%) mężczyzn (średni wiek $65,8 \pm 9,6$ roku), z napadowym (51,3%) i przetrwałym (48,7%) migotaniem przedsionków. Średni czas trwania arytmii wynosił 4 lata Q1: 2, Q3: 7 (Q: kwartyli). U wszystkich chorych wykonano 2-wymiarowe badanie echokardiograficzne z funkcją Dopplera oraz pomiary stężeń BNP za pomocą testu immunoradiometrycznego na początku i po rocznej obserwacji.

Wyniki: W rocznej prospektywnej obserwacji u 15 (9,5%) pacjentów rozwinęła się utrwalona postać AF. W grupie chorych, u których nie stwierdzono utrwalonego AF, wyjściowe średnie stężenie BNP wynosiło: 41, Q1: 20, Q3: 81 pg/ml. Po roku średnia wynosiła 32,5; Q1: 20, Q3: 81 pg/ml. W grupie pacjentów, u których rozwinęło się utrwalone AF, średnie wyjściowe stężenie BNP wynosiło 96, Q1: 69, Q3: 151 pg/ml, natomiast po roku: 151,1, Q1: 97, Q3: 223 pg/ml. Różnica między grupami okazała się wysoce istotna statystycznie: wyjściowo — $p < 0,005$, po roku — $p < 0,0001$. Analiza parametrów echokardiograficznych w podgrupie chorych, u których doszło do utrwalenia się arytmii w przebiegu rocznej obserwacji, wykazała cechy dysfunkcji rozkurczowej lewej komory typu zaburzeń relaksacji.

Wnioski: Wśród chorych z nawracającym napadowym/przetrwałym AF utrzymujące się podwyższone osoczowe stężenie BNP i objawy dysfunkcji rozkurczowej lewej komory typu zaburzeń relaksacji mogą być czynnikami ryzyka przejścia AF w formę utrwaloną w krótkim czasie.

Słowa kluczowe: migotanie przedsionków, peptydy natriuretyczne, dysfunkcja rozkurczowa lewej komory, przebieg arytmii

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