Plasma NT-proANP in patients with persistent atrial fibrillation who underwent successful cardioversion

Radosław Bartkowiak[1], Beata Wożakowska-Kapłon[1, 2], Grażyna Janiszewska[3]

[1] 1st Department of Cardiology, Centre of Cardiology, Kielce, Poland
[2] Health Department, Jan Kochanowski University, Kielce, Poland
[3] Department of Medical Biochemistry, Medical University, Lodz, Poland

Abstract

Background: Atrial fibrillation (AF) decreases quality of life and significantly increases risk of stroke, congestive heart failure and death. Atrial overload and stretch also result in increased production of natriuretic peptide type A (ANP). The biologically inactive prohormone NT-proANP is released to plasma in the same amounts as ANP but it has higher levels in the blood due to decreased degradation in vivo. In vitro degradation is also slower and NT-proANP may be an interesting alternative for ANP.

Aim: To evaluate NT-proANP plasma concentration in patients with persistent AF following successful cardioversion.

Methods: The study group consisted of 43 patients with persistent AF and normal left ventricular systolic function, who underwent successful electrical cardioversion (EC). The control group comprised 20 patients with sinus rhythm without a history of AF. Blood samples were collected twice, during visits 24 h before and after EC. All patients were also examined 30 days after the sinus rhythm recovery. The NT-proANP concentration was measured using an immunochemical method (ELISA).

Results: Plasma NT-proANP concentration was significantly increased in patients with persistent AF compared to the control group (4.8 ± 2.9 vs. 2.8 ± 1.2 nmol/l, p = 0.004). Plasma NT-proANP level decreased significantly after successful cardioversion (to 3.2 ± 2.4 nmol/l; p < 0.0001). There was no correlation between the baseline NT-proANP concentration and sinus rhythm maintenance during 30 days after EC.

Conclusions: Plasma NT-proANP concentration is higher in patients with persistent AF and normal left ventricular systolic function than in patients without arrhythmia. Sinus rhythm recovery due to EC leads to a decrease of plasma NT-proANP. The baseline NT-proANP level has no prognostic value for prediction of sinus rhythm maintenance during 30 days after EC.

Key words: NT-proANP, atrial fibrillation, cardioversion

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Introduction

Epidemiological data show increasing prevalence of atrial fibrillation (AF) in the adult population [1]. Development of this arrhythmia, including paroxysmal, persistent, and permanent AF, leads to decreased quality of life, worsening of heart failure symptoms, and increased risk of stroke and death [2-4]. According to the current European and Polish guidelines, prevention of thromboembolic complications and appropriate rate control are indicated in all patients with AF [5]. In addition, restoration and long-term maintenance of sinus rhythm may be attempted in some patients. The choice of the treatment strategy is a major initial decision in the management of these patients that should be made on an individual basis, taking into account the type, severity and frequency of clinical symptoms, patient preference, coexisting conditions, and response to therapy.

These management decisions might be helped by identification of a subgroup of patients with AF who would benefit most from the rhythm control strategy. However, predicting long-term effectiveness of cardioversion based on available clinical and echocardiographic data has been difficult. Thus, new prognostic markers, including biochemical parameters, are currently being investigated to help in more precise clinical evaluation of the constantly growing population of patients with AF.

The first discovered neurohormone secreted by the heart was the A-type natriuretic peptide (ANP), initially called atrial

Address for correspondence:
Beata Wożakowska-Kapłon MD, PhD, I Kliniczny Oddział Kardiologii, Świętokrzyskie Centrum Kardiologii, ul. Grunwaldzka 45, 25-736 Kielce, tel.: +48 41 367 13 01, e-mail: bw.kaplon@poczta.onet.pl

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natriuretic peptide due to its predominant synthesis in the atria. This natriuretic peptide is released into the blood and circulates as longer, biologically inactive N-terminal fragments, known as N-terminal pro-A-type natriuretic peptide (NT-proANP), and biologically active, shorter peptides (ANP) [6].

The A-type natriuretic peptide is synthesised and secreted mainly by atrial cardiomyocytes in response to atrial dilatation [7]. Long-lasting AF leads to a decrease in ANP level due to progressive pathological atrial remodelling [8-10]. Thus, ANP may serve as a marker of normal atrial function and might be helpful in identification of appropriate candidates for therapeutic interventions, such as those aiming to restore and maintain sinus rhythm [8]. In contrast, the clinical value of NT-proANP in AF remains undetermined due to a lack of studies measuring blood levels of this propeptide in patients with AF. Biologically inactive NT-proANP is released in amounts equivalent to those of ANP but is characterised by a significantly longer half-time in circulation and thus its plasma level is approximately 50 times higher than that of active ANP [6]. An advantage of NT-proANP is slower degradation seen both in vivo and in vitro, resulting in higher stability of blood levels. Thus, plasma NT-proANP level as a marker of atrial function may be an interesting alternative to ANP. The purpose of this study was to evaluate plasma NT-proANP level using an immunoenzymatic method in patients with persistent AF before and after a successful electrical cardioversion.

Methods

Study group

The study group consisted of patients with persistent AF who underwent successful electrical cardioversion (EC) resulting in restoration of sinus rhythm. The main inclusion criteria were: persistent non-valvular AF, no contraindications to restoration of sinus rhythm with EC, preserved left ventricular (LV) systolic function as determined by echocardiography [LV ejection fraction (LVEF) > 50%], absence of heart failure symptoms, and well-controlled underlying disease (hypertension, coronary artery disease, diabetes). Exclusion criteria included lack of patient consent for participation in the study, reversible or transient cause of the arrhythmia, and inability to evaluate LV systolic function precisely using transthoracic echocardiography. The control group consisted of 20 patients of similar age and gender distribution, hospitalised due to cardiovascular diseases, but without symptoms of heart failure and with preserved sinus rhythm and no history of AF.

All participants were evaluated during three visits, 24 h before and after EC, and at 30 days following sinus rhythm restoration. These visits included clinical evaluation, echocardiography, and recording of an electrocardiogram (ECG). The NT-pro-ANP level was determined 24 h before and after EC.

The study was approved by the local Ethics Committee (approval no. 30/2004). All participants were informed in detail about the purpose and the conduct of the study, and all gave written consent for participation in the study. Separate patient consent was obtained before each EC procedure.

Electrical cardioversion procedure

To restore sinus rhythm, EC was performed during short-term general anaesthesia with a biphasic impulse generated using a Physio-Control Lifepak 12 device (Medtronic). The impulses were synchronised with R waves of an ECG tracing, and cardioverter paddles were placed in the anteroapical position. The initial impulse energy was 100 J and if unsuccessful, EC was attempted up to two times with a 200 J impulse. Total impulse energy was up to 500 J. Successful EC was defined as no AF recurrence during 24 h following EC. Early EC outcomes were evaluated at 30 days. Depending on the presence or absence of sinus rhythm in the ECG recorded during the follow-up visit at 30 days, and the history of AF recurrence during the 30 days documented with either conventional or Holter ECG, participants were divided into two subgroups: patients without arrhythmia recurrence, and a subgroup with recurrent AF.

Echocardiographic study

Transthoracic echocardiography was performed using a digital Acuson Sequoia C 256 device (Siemens) and a 2.5--3.5 MHz probe. All standard echocardiographic parameters were evaluated, with particular reference to LVEF and left atrial dimensions.

NT-proANP determination

Blood for NT-proANP level assessment was collected in the morning hours in supine fasting patients from an antecubital vein to test tubes coated with EDTA. The collected blood was subsequently centrifuged in the hospital laboratory at 4°C and plasma was frozen at –25°C. Plasma NT-proANP level was measured immunoenzymatically using proANP (1-98) ELISA No. BI-20892 kits (Biomedica). NT-proANP level measurements were performed in the Department of Medical Biochemistry at the Medical University of Lodz.

Antiarrhythmic drug therapy was used in most patients following successful EC. The choice of an antiarrhythmic drug was made in accordance with the current European Society of Cardiology guidelines in regard to the rhythm control strategy [5].

Statistical methods

Arithmetic means and standard deviations were calculated for the evaluated parameters. The Student *t*-test for unpaired values was used to compare mean values of normally distributed parameters, and the Wilcoxon test was used to compare mean values of non-

Table I. Clinical characteristics of patients with AF and the control group

Parameter	Persistent AF n = 43 X ± SD	Controls n = 20 X ± SD	p
Age [years]	59.0 ± 11.6	57.1 ± 10.4	NS
Gender, n (%)			
women	8 (18.6)	4 (20)	NS
men	35 (81.4)	16 (80)	
BMI [kg/m^2], n (%)			
normal (BMI < 25)	5 (11.6)	5 (25)	0.01
overweight (BMI 25-29)	19 (44.2)	8 (40)	0.56
obesity (BMI ≥ 30)	19 (44.2)	7 (35)	0.13
Heart rate [beats/min]	85.4 ± 13.0	78.5 ± 13.0	NS
Systolic blood pressure [mmHg]	130.6 ± 14.9	135.3 ± 20.7	NS
Diastolic blood pressure [mmHg]	80.3 ± 9.0	82.5 ± 8.5	NS
Coexisting conditions, n (%)			
hypertension	27 (62.8)	16 (80)	<0.01
coronary artery disease	8 (18.6)	6 (30)	0.07
diabetes	3 (7.0)	7 (35)	0.01
COPD	2 (4.6)	1 (5)	0.50

Abbreviations: BMI – body mass index, COPD – chronic obstructive pulmonary disease

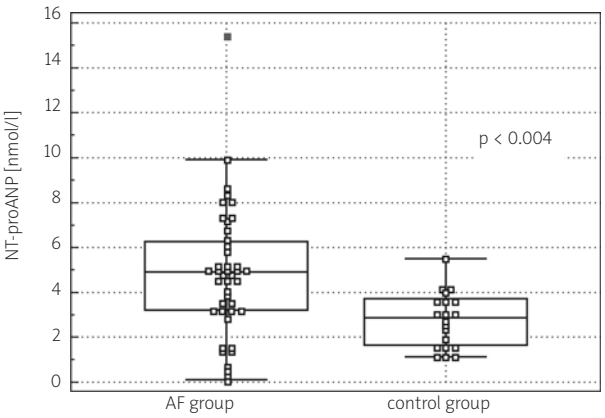

Figure 1. Individual baseline values of plasma NT-proANP level in the AF and control groups

normally distributed parameters. The χ^2 test was used to compare rates of specific values of categorical variables in the study groups.

Correlations between normally distributed parameters were evaluated using the Pearson linear correlation coefficient, and correlation between non-normally distributed parameters using the Spearman correlation coefficient. Logistic regression analysis was used to determine the prognostic value of selected variables. The level of statistical significance was set at $p < 0.05$.

Distribution of blood levels of selected biomarkers was illustrated with box-and-whisker plots showing minimal value, lower quartile, median, upper quartile, maximal value, and outliers.

Statistical analyses were performed using SYSTAT software, version 7.0 (licence No. 1893885), and MedCalc software, version 4.16g.

Results

Initially, 45 patients aged 18-75 years were considered for participation in the study. As EC did not succeed in restoration of sinus rhythm in two patients, the study group finally consisted of 43 patients, including 35 men and 8 women. The mean age was 59.0 ± 11.8 years. Duration of AF ranged from 7 days to 20 months (mean 12.3 ± 15.3 weeks). In our study group, the main risk factors for AF occurrence were hypertension, ischaemic heart disease, and diabetes. Lone AF was diagnosed in some patients below 60 years of age without coexisting cardiovascular disease.

Patients in the control group were more frequently affected with hypertension (80 vs. 62.8%, p = 0.002) and diabetes (35 vs. 7%, p = 0.0001).

Physical examination during the initial visit in patients with AF revealed a mean heart rate of 85.4 ± 13.2 bpm. During that visit, the mean recorded systolic blood pressure was 130.6 ± 15.1 mmHg, and the mean diastolic blood pressure was 80.3 ± 9.1 mmHg. The LV systolic function was normal, with a mean LVEF of 57.3 ± 6.1%. The maximum transverse diameter of the left atrium as determined in the parasternal M-mode view was 43.7 ± 5.9 mm and did not differ significantly from the mean value in the control group (41.5 ± 4.1 mm, NS).

The clinical characteristics of patients with persistent AF and the control group are shown in Table I.

Plasma NT-proANP level in patients with persistent AF was 4.8 ± 2.9 nmol/L, significantly higher than in controls (2.8 ± 1.2 nmol/l, p = 0.004). Figure 1 shows individual NT-proANP values in the study and control groups. In patients with AF plasma NT-proANP level measured 24 h after sinus rhythm restoration was significantly reduced compared to the level measured 24 h before EC (3.2 ± 2.4 vs. 4.8 ± 2.9 nmol/l; p < 0.0001). On average, plasma NT-proANP level was reduced by 33% during the first 24 h after EC. The distribution of NT-proANP values in the AF group 24 h before and after EC is shown in Figure 2.

Early EC outcomes were evaluated at 30 days. Sinus rhythm was present in all participants at 24 h after EC, while after 30 days sinus rhythm was maintained without any documented AF recurrence in 24 (56%) patients. Depending on the presence or absence of sinus rhythm in the ECG recorded during the follow-up visit at 30 days after EC, and the history of AF recurrence documented during the 30 days of follow-up, participants were divided into two subgroups – patients with or without AF recurrence.

These two subgroups did not differ in regard to baseline clinical and echocardiographic parameters evaluated before EC. No significant differences were found

in the prevalence of coexisting cardiovascular diseases (coronary artery diseases, hypertension, and previous stroke) and diabetes. The two subgroups did not differ in regard to the antiarrhythmic drug therapy prescribed after EC. Finally, no differences in the rate of angiotensin-converting enzyme inhibitor and statin use after EC were seen between the two groups (Table II).

Plasma NT-proANP level measured before EC did not differ significantly between patients with or without AF recurrence (5.1 ± 3.5 vs. 4.4 ± 2.0 nmol/l, respectively, p = 0.48). In addition, logistic regression analysis showed no significant relationship between baseline plasma NT-proANP level and the maintenance of sinus rhythm at 30 days after EC (p = 0.47). We also evaluated the relationship between the observed change in plasma NT-proANP level during the first 24 h after sinus rhythm restoration and early EC outcomes at 30 days. A significant reduction in plasma NT-proANP level during the first 24 h after EC was seen both in patients maintaining sinus rhythm (from 5.1 ± 3.5 nmol/L before EC to 3.4 ± 2.6 nmol/l after EC) and in those with AF recurrence (from 4.4 ± 2.0 nmol/l before EC to 3.0 ± 2.3 nmol/l after EC). Similarly, logistic regression analysis showed no significant relationship between the change in plasma NT-proANP level and the maintenance of sinus rhythm at 30 days after EC. The results of plasma NT-proANP level in both subgroups before and after EC are shown in Figure 3.

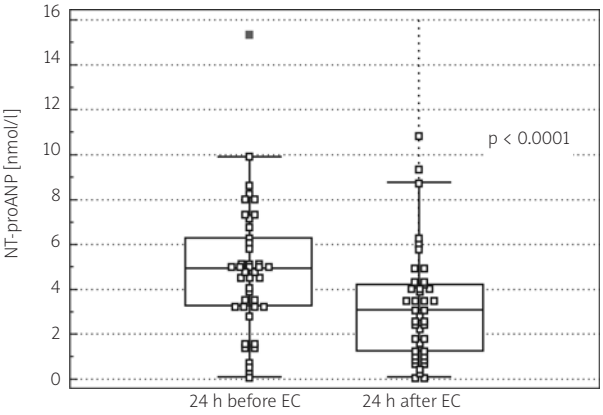

Figure 2. Individual values of plasma NT-proANP level in patients with AF determined 24 h before and after EC

Table II. Clinical characteristics of patients with persistent AF divided into subgroups depending on the early outcomes of EC

Parameter	Sinus rhythm n = 24 X ± SD	AF recurrence n = 19 X ± SD	p
1. Age [years]	60.1 ± 10.3	57.7 ± 13.6	NS
2. Gender, n (%)			
men	21 (87.5)	14 (73.7)	NS
women	3 (12.5)	5 (26.3)	
3. BMI [kg/m^2], n (%)			
normal (BMI < 25)	2 (8.3)	3 (15.8)	NS
overweight (BMI 25-29)	12 (50.0)	7 (36.8)	
obesity (BMI ≥ 30)	10 (41.7)	9 (47.4)	
4. Heart rate [beats/min]	85.5 ± 13.7	85.3 ± 12.9	NS
5. Systolic blood pressure [mmHg]	133.2 ± 14.5	127.4 ± 15.7	NS
6. Diastolic blood pressure [mmHg]	81.1 ± 9.5	79.2 ± 8.7	NS
7. Coexisting conditions, n (%)			
hypertension	16 (66.7)	11 (57.9)	NS
ischaemic heart disease	6 (25.0)	2 (10.5)	
diabetes	1 (4.2)	2 (10.5)	
8. Lone AF, n (%)	5 (20.8)	4 (21.1)	NS
9. Mean duration of AF [weeks]	12.6 ± 18.1	12.0 ± 11.0	NS
10. Antiarrhythmic drugs used after EC, n (%)			
amiodarone	10 (41.7)	6 (31.6)	NS
propafenone	11 (45.8)	8 (42.1)	
sotalol	1 (4.2)	1 (5.3)	
beta-blockers	15 (62.5)	11 (57.9)	
11. Other drugs used after EC, n (%)			
ACE inhibitor	17 (70.8)	16 (84.2)	NS
statin	10 (41.7)	12 (63.2)	

Abbreviations: ACE – angiotensin-converting enzyme, BMI – body mass index

Discussion

Data available in the literature clearly show that ANP level in patients with AF is significantly higher compared to patients of similar clinical characteristics who remain in sinus rhythm [11, 12]. Mechanisms responsible for increased ANP release in AF have not been clearly elucidated. Already in the first minutes after the occurrence of AF, ANP is released to the circulating blood in increased amounts in response to volume overload [13]. The main factor regulating ANP release from cardiomyocytes is atrial wall tension. With the increase in atrial wall tension, ANP release is enhanced [14]. Increased atrial wall tension usually results from enhanced intra-atrial pressure. During AF, increased intra-atrial pressure is related to abnormal atrial emptying due to a lack of haemodynamically effective atrial contraction. Some authors have also noted a relationship between ventricular rate and ANP level in patients with AF [15, 16]. Our findings show that also NT-proANP level is significantly higher in patients with persistent AF compared to patients who remain in sinus rhythm. These results are in agreement with data regarding plasma ANP level in patients with AF presented in other studies [8-10, 17, 18]. A novel aspect of our study is determination of inactive NT-proANP (present in a higher level in blood and more stable in vivo and in vitro than biologically active ANP) using an immunoenzymatic method (ELISA) that is less time-consuming and has fewer limitations compared to radioimmunological assays.

Our findings show that increased plasma NT-proANP level resulting from persistent AF is reversible shortly after restoration of sinus rhythm. Other authors have shown that the return of sinus rhythm, either spontaneously or by cardioversion, is associated with a significant decrease in ANP level [16-19]. Arakawa et al. [17] and Fujiwara et al. [20] observed a decrease in ANP level already in the first few minutes following a successful cardioversion. Mookherjee et al. [21] showed normalisation of plasma ANP level following a successful cardioversion regardless of the presence of heart failure. These studies also shown that unsuccessful EC did not result in any significant changes in ANP level [17, 20, 21]. Thus, it seems that EC itself as a procedure involving the use of an electrical impulse does not affect plasma levels of natriuretic peptides, and concordant changes in NT-proANP and ANP levels can be seen following successful cardioversion. It is likely that major factors leading to decreased release of NT-proANP and ANP, thus subsequently resulting in reduced plasma levels of these peptides, are lower heart rate and stabilisation of cardiac rhythm. The observed changes may also result from transient secretory insufficiency of atrial cardiomyocytes due to reduced sensitivity of atrial receptors to the stimuli normally resulting in ANP release [16].

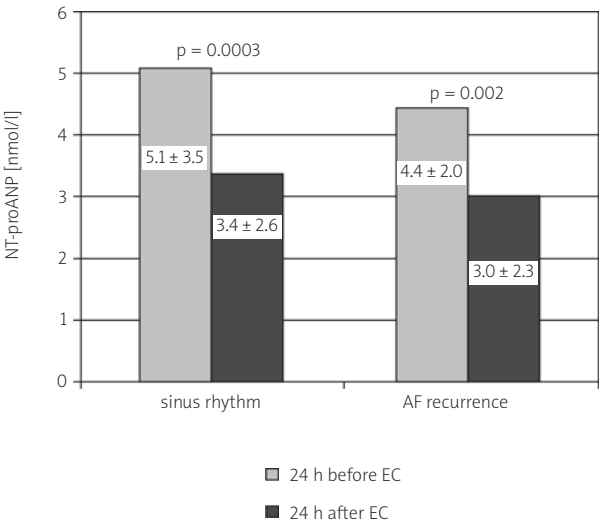

Figure 3. Comparison of mean plasma NT-proANP levels before and after EC in patients maintaining sinus rhythm and in those with AF recurrence

Appropriate choice between rhythm control and rate control strategies in the management of AF might spare repeated cardioversion procedures and numerous adverse effects of antiarrhythmic drug therapy in patients in whom long-term maintenance of sinus rhythm cannot be expected. The search for easy-to-use markers of early and long-term effectiveness of cardioversion has been ongoing for years. Mattioli et al. [8] showed a high likelihood of spontaneous sinus rhythm return in patients with high plasma ANP level during AF. As suggested by these authors, high plasma ANP level during AF predicts the success of cardioversion, and low plasma ANP level, more commonly seen in long-lasting AF, is a predictive factor of limited success of cardioversion attempts [8-10]. Accumulating evidence suggests that a decrease in ANP level during long-lasting AF results from adverse structural changes in the atria [22-25]. Natriuretic peptides most likely have no direct effect on cardiac rhythm but reflect haemodynamic milieu affected by changes in cardiac rhythm that occur with time. Atria that are structurally and physiologically able to sustain sinus rhythm differ from those in which AF recurs or becomes permanent. Natriuretic peptides, and in particular ANP and NT-proANP, which are synthesised mainly in the atria, are sensitive markers of these changes that might allow differentiation between various stages of the disease process involving these cardiac chambers.

In our study, we did not observe any relationship between baseline plasma NT-proANP level and the maintenance of sinus rhythm after 30 days of follow-up. Although plasma NT-proANP level tended to be higher in patients without AF recurrence, this difference did not reach statistical significance. A limitation of our analysis was the small number of participants. Hornestam et al. [26] also showed that NT-proANP level is a biochemical marker of increased intra-atrial pressure but does not predict sinus rhythm return. No significant prognostic value of baseline

plasma ANP level determined using a radioimmunological assay as a predictor of the maintenance of sinus rhythm following EC in patients with persistent AF was also found in a study by Wożakowska-Kapłon et al. [27]. In conclusion, although it seems that the prognostic value of measurements of atrial natriuretic peptides in patients with AF is limited, plasma NT-proANP level determinations using ELISA may be an attractive alternative approach to less convenient, more time-consuming and more expensive radioimmunological ANP assays in this patient population.

Conclusions

In patients with persistent AF and normal left ventricular systolic function, plasma NT-proANP level determined using ELISA is significantly higher compared to patients without AF. Successful EC leads to a decrease in plasma NT-proANP level already in the first 24 h following restoration of sinus rhythm, however, baseline NT-proANP concentrations is not predictive for a mid-term sinus rhythm maintioned.

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Ocena stężenia NT-proANP w osoczu, oznaczanego metodą immunoenzymatyczną, u chorych z przetrwałym migotaniem przedsionków po skutecznej kardiowersji

Radosław Bartkowiak[1], Beata Wożakowska-Kapłon[1, 2], Grażyna Janiszewska[3]

[1] I Kliniczny Oddział Kardiologii, Świętokrzyskie Centrum Kardiologii, Kielce
[2] Wydział Nauk o Zdrowiu, Uniwersytet Humanistyczno-Przyrodniczy Jana Kochanowskiego, Kielce
[3] Zakład Biochemii Medycznej, Uniwersytet Medyczny, Łódź

Streszczenie

Wstęp: Migotanie przedsionków (AF) prowadzi do pogorszenia jakości życia, nasila objawy niewydolności serca, zwiększa ryzyko udaru mózgu i zgonu. Przeciążenie oraz rozciągnięcie przedsionków w przebiegu AF prowadzą do zwiększenia produkcji i uwalniania do krwi peptydu natriuretycznego typu A (ANP). Nieaktywny biologicznie prohormon NT-proANP jest wydzielany w równych ilościach z ANP, ale ma istotnie wyższe stężenie w osoczu i z uwagi na wolniejszą degradację *in vitro* może stanowić interesującą alternatywę dla oznaczania ANP.

Cel: Badanie stężenia NT-proANP w osoczu, oznaczanego metodą immunoenzymatyczną, u chorych z przetrwałym AF przed kardiowersją elektryczną (KE) i po jej skutecznym przeprowadzeniu.

Metody: Grupę badaną stanowiło 43 chorych z przetrwałym AF o etiologii niezastawkowej, z prawidłową czynnością skurczową lewej komory (funkcja skurczowa lewej komory w badaniu echokardiograficznym > 50%), bez objawów klinicznych niewydolności serca, z dobrze kontrolowaną chorobą podstawową (nadciśnienie tętnicze, choroba wieńcowa, cukrzyca), bez przeciwwskazań do KE, u których przywrócono rytm zatokowy. Grupę kontrolną stanowiło 20 osób bez AF w wywiadzie. U chorych wykonano badanie kliniczne, echokardiograficzne i oznaczenia NT-proANP 24 godz. przed KE, 24 godz. po KE oraz w 30. dobie od przywrócenia rytmu zatokowego.

Wyniki: Stężenie NT-proANP w osoczu chorych z przetrwałym AF było istotnie większe w porównaniu z grupą kontrolną (4,8 ± 2,9 *vs* 2,8 ± 1,2 nmol/l, p = 0,004). Stwierdzono istotne zmniejszenie stężenia NT-proANP w osoczu 24 godz. po przywróceniu rytmu zatokowego (3,2 ± 2,4 nmol/l, p < 0,0001). Nie wykazano związku pomiędzy stężeniem NT-proANP w trakcie AF a utrzymaniem rytmu zatokowego w okresie 30 dni po kardiowersji.

Wnioski: U chorych z przetrwałym AF oraz prawidłową funkcją skurczową lewej komory stężenie NT-proANP w osoczu, oceniane metodą ELISA, jest istotnie wyższe w porównaniu z grupą osób bez tej arytmii. Skuteczna KE prowadzi do obniżenia stężenia NT-proANP już w pierwszej dobie po przywróceniu rytmu zatokowego.

Słowa kluczowe: NT-proANP, migotanie przedsionków, kardiowersja elektryczna

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Adres do korespondencji:
dr hab. n. med. Beata Wożakowska-Kapłon, I Kliniczny Oddział Kardiologii, Świętokrzyskie Centrum Kardiologii, ul. Grunwaldzka 45, 25-736 Kielce, tel.: +48 41 367 13 01, e-mail: bw.kaplon@poczta.onet.pl

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