

# B-type natriuretic peptide level after sinus rhythm restoration in patients with persistent atrial fibrillation — clinical significance

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## Abstract

**Background:** Persistent atrial fibrillation (AF) leads to electrical, structural and neurohormonal remodelling of the atria, including increased plasma B-type natriuretic peptide (BNP) level.

**Aim:** To assess the clinical value of plasma BNP or NT-proBNP concentrations in patients with persistent AF measured before and after sinus rhythm restoration following direct-current cardioversion.

**Methods:** The study group consisted of 43 patients with persistent AF who underwent successful electrical cardioversion. The mean AF duration was 12.3 weeks. Patients in the study group had no symptoms of heart failure and they had preserved left ventricular systolic function. Blood samples were collected twice: 24 hours before and 24 hours after electrical cardioversion. Logistic regression analysis was used to assess the predictive value of BNP and NT-proBNP levels.

**Results:** Baseline NT-proBNP and BNP levels were increased in patients with persistent AF ( $290.9 \pm 257.2$  pg/mL and  $148.4 \pm 111.4$  pg/mL, respectively) compared to a matched control group without AF ( $47.8 \pm 80.6$  pg/mL;  $p = 0.0001$  and  $74.9 \pm 81.7$  pg/mL;  $p = 0.01$ ). Plasma BNP level decreased 24 hours after cardioversion (from  $148.4 \pm 111.4$  to  $106.4 \pm 74.7$  pg/mL;  $p = 0.0045$ ) whereas NT-proBNP level did not (from  $290.9 \pm 257.2$  to  $262.7 \pm 185.6$  pg/mL; NS). During an 18-month follow-up period, 21 (49%) patients remained in sinus rhythm. Neither baseline plasma BNP nor NT-proBNP level predicted sinus rhythm maintenance.

**Conclusions:** NT-proBNP and BNP plasma levels are increased in patients with persistent AF. Conversion to sinus rhythm is associated with a significant decrease in plasma BNP but not NT-proBNP level. Baseline BNP and NT-proBNP levels do not predict long-term sinus rhythm maintenance.

**Key words:** BNP, NT-proBNP, atrial fibrillation, direct current cardioversion

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## INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. It is characterised by disorganised atrial activation leading to impaired mechanical function [1]. The presence of AF is associated with increased risk of stroke [2], heart failure (HF), and death [3, 4]. Management of AF inclu-

des prevention of thromboembolic complications, appropriate rate control to decrease the risk of tachycardia-induced cardiomyopathy, and rhythm control with attempts to restore and maintain sinus rhythm [5].

Restoration of sinus rhythm leads to return of atrial mechanical function and improved left ventricular (LV) function.

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However, adverse effects of antiarrhythmic drugs and repeated electrical cardioversions (EC) lead to decreased quality of life of patients managed with rhythm control strategy, and this treatment has not been shown to decrease mortality. Thus, optimal management of patients with AF requires individualised approach, taking into account the underlying pathology.

Evaluation of changes in selected neurohormonal markers in persistent AF and following sinus rhythm restoration may lead to better understanding of the pathophysiology of this arrhythmia and help in predicting its clinical course and response to treatment. The purpose of this study was to measure and compare plasma levels of B-type natriuretic peptide (BNP) and its propeptide N-terminal fragment (NT-proBNP) before and after sinus rhythm restoration in patients with persistent AF and preserved LV systolic function, and to evaluate clinical value of these parameters as prognostic factor of sinus rhythm maintenance following direct current EC.

## METHODS

### Patients

The study group consisted of patients with persistent nonvalvular AF with preserved LV systolic function and no clinical symptoms of HF in whom sinus rhythm was restored with EC. The main inclusion criteria were: persistent nonvalvular AF, no contraindications to EC, good LV systolic function by echocardiography [LV ejection fraction (LVEF) > 50%], absent HF symptoms, and well-controlled underlying disease (hypertension, coronary artery disease, diabetes). The exclusion criteria included lack of patient consent for the participation in the study, a reversible or transient cause of the arrhythmia, and inability to evaluate LV systolic function precisely in the transthoracic echocardiography.

The control group consisted of 20 patients of similar age and gender distribution, hospitalised due to a cardiovascular disease but without symptoms of HF, with sinus rhythm and no history of AF [6]. All patients included in the study were evaluated 24 hours before and after EC. Repeated evaluation of cardiac rhythm was performed at 18 months after cardioversion based on physical examination and ECG recording.

Most patients received antiarrhythmic drugs following successful EC. The choice of the antiarrhythmic drug was based on the current European Society of Cardiology guidelines regarding pharmacological rhythm control in patients with AF [5].

The study was approved by the local ethics committee (approval No. 30/2004) [6]. Written informed consent was obtained from all patients who had been instructed in detail regarding the purpose and conduct of the study. A separate written consent was obtained before each EC procedure.

### Electrical cardioversion

To restore sinus rhythm, EC was performed in short-lasting general anaesthesia using biphasic DC impulse (Medtronic Physio-Control Lifepak 12) synchronised with the R waves of the ECG. Anterolateral position of the paddles was used. Ini-

tial impulse energy was 100 J, and if unsuccessful, cardioversion with a 200 J impulse was attempted twice. Maximal cumulative energy output during one EC procedure was 500 J. Successful EC was defined as the lack of AF recurrence within 24 hours.

### Echocardiography

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

### Biochemical evaluation

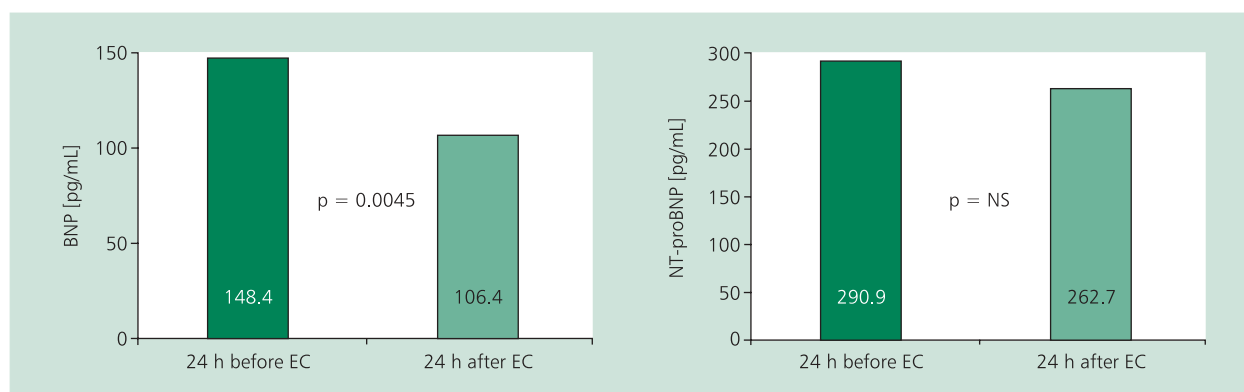
Blood for determination of NT-proBNP and BNP levels was drawn in the morning, in fasting and supine patients, 24 hours before and after EC. Blood was collected by antecubital vein puncture and drawn into test tubes coated with EDTA. Blood was then centrifuged in the hospital laboratory at 4°C and plasma was frozen at 25°C. Plasma NT-proBNP level was determined immunoenzymatically using the NT-proBNP ELISA No. BI-20852 kit (Biomedica). Upper reference values of plasma NT-proBNP level as determined by the manufacturer are 84 pg/mL in men and 146 pg/mL in women, respectively. Plasma BNP level 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. Determinations were performed in the Department of Clinical Biochemistry at the Medical University of Łódź.

### Statistical analysis

We calculated arithmetical means and standard deviations of the evaluated parameters. Unpaired Student *t* test was used to compare mean values of normally distributed variables, and the Wilcoxon test was used to compare mean values of non-normally distributed variables. Frequencies of distribution of parametric variables in the study group were compared using  $\chi^2$  test. To test correlations, the Pearson linear correlation coefficient was used for normally distributed variables of equal variance, and the Spearman coefficient was used for non-normally distributed variables. Logistic regression analysis was used to evaluate the prognostic value of BNP and NT-proBNP levels as predictors of short- and long-term EC outcomes. A *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using SYSTAT version 7.0 and MedCalc version 4.16 programmes.

## RESULTS

Initially, 45 patients aged 18–75 years were recruited to the study. In two patients, however, EC was unsuccessful and the study group finally consisted of 43 patients, including 35 men and 8 women. The mean age of the patients was  $59.0 \pm 11.8$  years, and the duration of AF ranged from 7 days to 20 months (mean  $12.3 \pm 15.3$  weeks). The main risk factors



**Figure 1.** Mean BNP and NT-proBNP level 24 hours before and after electrical cardioversion (EC).

of AF in the study group were hypertension (in 63% of patients), coronary artery disease (in 19%), and diabetes (in 7%). Lone AF was diagnosed in 21% patients who were aged less than 60 years and had no coexisting cardiovascular disease. The mean ventricular rate was  $85.4 \pm 13.2$  bpm, and the mean blood pressure was  $130.6 \pm 15.1/80.3 \pm 9.1$  mm Hg. Mean LVEF was  $57.3 \pm 6.1\%$ . Maximal transverse left atrial dimension in M-mode parasternal view was  $43.7 \pm 5.9$  mm, and the end-diastolic LV diameter was  $52 \pm 5.1$  mm.

Plasma BNP level in patients with persistent AF was  $148.4 \pm 111.4$  pg/mL, and plasma NT-proBNP level was  $290.9 \pm 257.2$  pg/mL, both values being significantly higher compared to the control group ( $74.9 \pm 81.7$  pg/mL,  $p = 0.01$ ; and  $47.8 \pm 80.6$  pg/mL,  $p = 0.0001$ , respectively). We attempted to identify parameters that significantly affected plasma BNP and NT-proBNP level in patients with persistent AF and no symptoms of HF. We found a significant correlation between age and plasma BNP and NT-proBNP level in our study group. For BNP level, the Pearson linear correlation coefficient was 0.43 ( $p = 0.02$ ), and the Spearman correlation coefficient was 0.54 ( $p = 0.002$ ). For NT-proBNP level, the Pearson linear correlation coefficient was 0.54 ( $p = 0.002$ ), and the Spearman correlation coefficient was 0.62 ( $p < 0.0001$ ). We found no association between the duration of arrhythmia (mean 12.3 weeks) and BNP and NT-proBNP levels. Regarding remaining clinical parameters, plasma BNP level only correlated with blood pressure. We found no association between plasma BNP and NT-proBNP levels and any of the evaluated echocardiographic parameters (LVEF, LV size, left atrial size, muscle mass) in the study group.

In patients with persistent AF who underwent EC, we found a significant decrease in plasma BNP level at 24 hours after sinus rhythm restoration compared to the values measured during the arrhythmia. In contrast, plasma NT-proBNP level at 24 hours after sinus rhythm restoration did not differ significantly compared to pre-cardioversion values (Fig. 1).

**Table 1.** Logistic regression analysis regarding the prognostic value of BNP and NT-proBNP levels as predictors of sinus rhythm maintenance at 18 months

Parameter	$\chi^2$	P
BNP before cardioversion	1.7	0.084
BNP after cardioversion	1.1	0.25
NT-proBNP before cardioversion	0.8	0.13
NT-proBNP after cardioversion	2.5	0.05

At 18-month follow-up, sinus rhythm was present in 21 (48%) patients. Logistic regression analysis showed no relation between baseline BNP and NT-proBNP levels and sinus rhythm maintenance 18 months after EC (Table 1).

## DISCUSSION

Previously published studies showed increased BNP level in patients with AF and its decrease or return to normal values following sinus rhythm restoration [7, 8]. These studies were performed in small groups of subjects and mostly evaluated levels of biologically active natriuretic peptides. A novel aspect of the present study is a direct comparison of changes in BNP and NT-proBNP levels using immunoenzymatic ELISA method which is less time-consuming and has less limitations compared to radioimmunologic methods [9].

In our study, age and blood pressure correlated positively with BNP and NT-proBNP levels, as was previously shown in populations in sinus rhythm. In contrast, no correlation between BNP and NT-proBNP levels and LV size and LVEF in our study may be most likely explained by the fact that these echocardiographic parameters were normal in our subjects. Our findings confirm an association between AF and the release of BNP and NT-proBNP. B-type natriuretic peptide is a peptide released by cardiac ventricles in response to volume and pressure overload [10, 11]. Increased pressure in fibrillating atrial results in increased wall tension and induces

BNP gene expression in both ventricles and atria [12]. Two mechanisms regulating BNP release in AF are probably operating: release of the contents of atrial cardiomyocyte granules in patients without LV dysfunction and de novo synthesis in ventricular cardiomyocytes [13]. Our study, in which BNP levels were determined in patients without HF symptoms and with no LV systolic dysfunction, suggests an independent effect of the arrhythmia on the secretion of this peptide.

Previous studies on BNP release in AF were mostly performed in patients with chronic HF and permanent AF. Fewer studies were performed in patients with persistent AF and no symptoms of HF. McCullough et al. [14] found that the occurrence of AF resulted in increased BNP level in patients without coexisting HF who had normal baseline BNP level during sinus rhythm. Ohta et al. [15] and Inoue et al. [8] found increased BNP release in response to the occurrence of arrhythmia in patients with lone AF.

In our previous studies, we showed that natriuretic peptide levels in patients with AF and preserved LV systolic function may differ significantly depending on LV diastolic function [16, 17]. In our patients with AF and preserved LV systolic function, BNP level decreased following EC only in patients with diastolic dysfunction but remained unchanged in patients with normal LV diastolic function. This heterogeneous response to EC may suggest that patients with impaired diastolic function may benefit most from sinus rhythm restoration and should be targeted for cardioversion attempts. Large heterogeneity of patients with AF may explain inconsistent results of published studies on natriuretic peptides. Of note, the heterogeneous response to successful EC in patients with impaired or preserved LV diastolic function was not seen for the other natriuretic peptide, i.e. atrial natriuretic peptide (ANP).

The NT-proBNP has no biological activity but is an interesting target for laboratory testing due to favourable analytic characteristics and possibility of reduced preanalytic errors, including high stability in collected specimens [18, 19]. Advantages of NT-proBNP testing include longer plasma half-life, fourfold higher plasma level compared to biologically active BNP, and *in vitro* stability of the measured substance. The NT-proBNP is secreted in equal amounts to BNP, and mechanism regulating its secretion is identical to those regulating BNP secretion. During AF, impaired hemodynamic function of both atria and ventricles induces pre-pro-BNP gene expression and increased secretion of equal amounts of NT-proBNP and BNP. Our findings indicate increased NT-proBNP secretion by cardiomyocytes during this arrhythmia.

Only a few studies were performed regarding NT-proBNP secretion in patients with AF, and they mainly included patients with impaired LV systolic function and symptoms of HF [20, 21]. Only Shelton et al. [22] showed, both in patients with underlying cardiovascular disease and in patients with lone AF, that plasma NT-proBNP level in patients with AF was increased compared to patients with preserved sinus rhythm.

Both BNP and NT-proBNP are established markers of HF. Increased NT-proBNP and BNP levels in persistent AF have important practical implications in the diagnosis of HF, as increased plasma levels of these biomarkers may result from the arrhythmia itself and should not necessarily be interpreted as indicating significant LV systolic and/or diastolic dysfunction. Our findings show similar utility of NT-proBNP and BNP determination in the evaluation of neurohormonal disturbances in patients with persistent AF.

Of note, we found no significant changes in NT-proBNP level but only a trend toward lower values during first 24 hours following EC. It should be emphasised, however, that the plasma half-life of NT-proBNP is much longer compared to BNP (60–120 min vs 15–20 min). Thus, plasma NT-proBNP level may remain elevated during first 24 hours following EC despite lower secretion of this propeptide by cardiomyocytes. Reduction of elevated plasma NT-proBNP level might be expected in the next days following successful EC.

Similar results in patients with persistent AF were published by Shin et al. [23] who showed significant reduction in the NT-proBNP level 11 days following EC in patients who remained in sinus rhythm, but no significant change in plasma NT-proBNP level measured within an hour following successful EC.

Assessment of the prognostic significance of natriuretic peptides in AF is even more difficult than defining their diagnostic utility. Search for predictors of successful cardioversion and sinus rhythm maintenance continues for years but has been largely inconclusive. Apart from the duration of the arrhythmia, no other clinical, echocardiographic, haemodynamic or hormonal variable has an established prognostic role. Evaluation of the neurohormonal profile in patients with AF and preserved LV systolic function may also not serve as a definitive basis for decision to proceed with cardioversion or give up further attempts of sinus rhythm restoration. In our study, we were unable to show a relationship between baseline BNP, NT-proBNP level and sinus rhythm maintenance at 18-month follow-up. In previous studies, we also did not find such an association for baseline ANP level [24]. However, studies to assess cardiac hormonal excretion reserve in response to exercise showed that significant increase in ANP level and stable BNP level predicted sinus rhythm maintenance at 6-month follow-up [25].

The B-type natriuretic peptide probably has no direct effect on cardiac rhythm but reflects hemodynamic conditions modified by the changing ventricular rhythm. Atria that are structurally and functionally able to sustain sinus rhythm differ from those in which AF recurs or becomes permanent. The NT-proBNP and BNP are sensitive markers of these changes and give insight into the severity of the atrial disease. However, the role of these parameters in the clinical evaluation of AF is still unclear, and with many unresolved issues it has fallen short of our expectations.

## CONCLUSIONS

The NT-proBNP and BNP levels are significantly increased in patients with persistent AF and preserved LV function. Age and blood pressure show strong positive correlation with plasma NT-proBNP and BNP levels. Conversion to sinus rhythm is associated with a significant decrease in plasma BNP but not NT-proBNP level at 24 hours. Baseline BNP and NT-proBNP levels do not predict sinus rhythm maintenance during 18-month follow-up.

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# Peptyd natriuretyczny typu B po przywróceniu rytmu zatokowego u chorych z przetrwałym migotaniem przedsionków — znaczenie kliniczne

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## Streszczenie

**Wstęp:** Migotanie przedsionków (AF) prowadzi do przebudowy elektrycznej, strukturalnej i neurohormonalnej przedsionków. W wyniku arytmii dochodzi do wzrostu stężenia osoczowego stężenia peptydu natriuretycznego typu B (BNP) oraz NT-proBNP w osoczu chorych z AF.

**Cel:** Celem pracy była ocena zmian osoczowego stężenia BNP i NT-proBNP po przywróceniu rytmu zatokowego u chorych z przetrwałym AF i zachowaną czynnością skurczową lewej komory, a także ocena wartości klinicznej tych pomiarów dla prognozowania utrzymania rytmu zatokowego po kardiowersji elektrycznej (KE).

**Metody:** Badaniem objęto grupę 43 chorych z przetrwałym AF, u których przywrócono rytm zatokowy za pomocą KE. Głównymi kryteriami włączenia do badania były: przetrwałe AF o etiologii niezastawkowej, brak przeciwwskazań do przywrócenia rytmu zatokowego za pomocą KE, dobra funkcja skurczowa lewej komory w badaniu echokardiograficznym (LVEF > 50%), brak objawów niewydolności serca, dobrze kontrolowana choroba podstawowa (nadciśnienie tętnicze, choroba wieńcowa, cukrzyca). Krew do oznaczenia BNP i NT-proBNP pobierano 24 godziny przed KE i po niej. Stężenie NT-proBNP w osoczu oznaczano za pomocą testu immunoenzymatycznego ELISA, stężenie BNP w osoczu oznaczano metodą immunoenzymatyczną, używając zestawu AxSYM firmy Abbott. Powtórnej oceny rytmu serca dokonywano na podstawie badania przedmiotowego i zapisu EKG, po 18 miesiącach od KE.

**Wyniki:** Stężenia BNP i NT-proBNP w osoczu chorych z przetrwałym AF były istotnie wyższe w porównaniu z odpowiednio dobraną grupą kontrolną bez wywiadu AF (odpowiednio:  $148,4 \pm 111,4$  pg/ml v.  $74,9 \pm 81,7$  pg/ml;  $p = 0,01$  oraz  $290,9 \pm 257,2$  pg/ml v.  $47,8 \pm 80,6$  pg/ml;  $p = 0,0001$ ). W badanej grupie wykazano silną dodatnią korelację między wiekiem i wartościami ciśnienia tętniczego a osoczowymi stężeniami BNP i NT-proBNP. Stwierdzono istotne zmniejszenie stężenia BNP w osoczu, oznaczonego 24 godziny po przywróceniu rytmu zatokowego ( $148,4 \pm 111,4$  pg/ml do  $106,4 \pm 74,7$  pg/ml;  $p = 0,0045$ ). Natomiast nie wykazano istotnego statystycznie obniżenia stężenia NT-proBNP po przywróceniu rytmu zatokowego w porównaniu z wartościami sprzed KE ( $290,9 \pm 257,2$  pg/ml do  $262,7 \pm 185,6$  pg/ml;  $p = \text{NS}$ ). W 18-miesięcznej obserwacji 21 (48%) pacjentów utrzymywało rytm zatokowy. W analizie regresji logistycznej nie wykazano związku między wyjściowym stężeniem BNP i NT-proBNP a utrzymaniem rytmu zatokowego po KE, w obserwacji 1,5-roczonej.

**Wnioski:** U chorych z przetrwałym AF z zachowaną funkcją skurczową lewej komory wykazano istotnie wyższe stężenia BNP i NT-proBNP. W 24. godzinie od przywrócenia rytmu zatokowego zaobserwowano istotne obniżenie stężenia BNP, natomiast nie wystąpiło znamienne statystycznie zmniejszenie stężenia NT-proBNP. Stężenia BNP i NT-proBNP w warunkach podstawowych nie było wskaźnikiem utrzymania rytmu zatokowego w 18-miesięcznej obserwacji.

**Słowa kluczowe:** BNP, NT-proBNP, migotanie przedsionków, kardiowersja elektryczna

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