

The effects of left ventricular diastolic function on natriuretic peptide levels after cardioversion of atrial fibrillation

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Abstract

Background: Diastolic heart failure often coexists with atrial fibrillation (AF). Elevated plasma levels of natriuretic peptides are the left ventricular (LV) marker of diastolic dysfunction.

Aim: To evaluate the influence of sinus rhythm restoration on ANP and BNP levels in patients with normal and impaired LV diastolic function.

Methods: The study included 42 patients (19 men, 23 women), aged 58.6 ± 8.2 years with non-valvular persistent AF with preserved LV systolic function who were successfully converted to sinus rhythm by DC cardioversion (CV) and maintained sinus rhythm for at least 30 days. On day 30 following CV in patients with sinus rhythm, Doppler echocardiography was performed to assess LV diastolic function. ECG, echocardiography, ANP and BNP plasma level measurements were made at baseline 24 h before CV and 24 h as well as 30 days after CV.

Results: The average ANP level in the whole study group during AF was 254.9 ± 79.9 pg/ml and the average BNP level was 113.6 ± 49.1 pg/ml. There was an evident decrease in ANP/BNP serum concentration in all the patients after successful DC cardioversion. Measured on the 30th day after CV, ANP and BNP levels were 153.2 ± 67.9 pg/ml and 61.9 ± 25.1 pg/ml respectively ($p < 0.001$). Thirty days after CV normal LV diastolic function was diagnosed in 15 patients and in 27 patients impaired diastolic function: 20 with impaired LV relaxation and 7 with impaired LV compliance. The extent of natriuretic peptides drop was dependent on the LV diastolic function, being more substantial in the subgroup with impaired LV diastolic function. In the subgroup with LV diastolic dysfunction the average ANP serum concentration measured 30 days after conversion was reduced by 111.2 ± 93.9 pg/ml (37%) ($p < 0.001$) and BNP level was reduced by 67.5 ± 36.0 pg/ml (46%) ($p < 0.001$). In patients with normal diastolic function sinus rhythm restoration significantly influenced ANP level, while having no relevant effect on BNP plasma concentration. The average ANP reduction in this subgroup was 64.4 ± 71.8 pg/ml (by 38%) and BNP reduction was 11.4 ± 16.7 pg/ml (by 23%) (NS).

Conclusions: The drop in ANP and BNP plasma concentrations after conversion to sinus rhythm in patients with AF depends on the LV diastolic function. Restoration of sinus rhythm is associated with improvement of the heart's haemodynamics, especially in patients with impaired LV diastolic function, which may be inferred from the more pronounced decrease of BNP level after DC cardioversion in this subgroup, as compared to that with normal LV function.

Key words: natriuretic peptides, diastolic dysfunction, atrial fibrillation

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Introduction

Diastolic heart failure (DHF) is universally accepted as a common cause of considerable cardiovascular morbidity and mortality [1]. It is estimated that 30-50% of patients with heart failure symptoms suffer from isolated diastolic dysfunction [2, 3]. According to the severity of DHF and the conditions that caused it, clinical manifestation is dominated by decreased compliance or impaired relaxation

of the left ventricle (LV). Most cardiovascular diseases begin with usually functional impairment of active ventricular relaxation, which is followed by structural changes in the heart muscle and shape of LV that may lead to decreased compliance. The most prevalent causes of DHF are hypertension, coronary heart disease, cardiomyopathies, diabetes, renal failure and structural changes in heart muscle in elderly patients [3].

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Diastolic heart failure often coexists with atrial fibrillation (AF) caused predominantly by atrial overload due to diastolic dysfunction and structural changes in atrial muscle engendered by main disease. Decline of atrial systolic activity, shortening of ventricular filling time and arrhythmia during AF are significant factors disturbing proper ventricular filling. Therefore new-onset AF in individuals with already impaired diastolic function of the heart becomes a crucial factor potentiating symptoms of DHF.

Recently, investigators have devoted much of their attention to the additive prognostic and diagnostic value of natriuretic peptides, especially BNP, in cardiovascular disorders. The group of natriuretic peptides is represented by atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP is produced mainly in atrial cardiomyocytes and BNP in ventricular myocardium and secondarily in atrial tissue. Both synthesis and secretion of natriuretic peptides are stimulated by increase of the atrial and ventricular muscle tone. Elevated plasma levels of ANP and BNP are associated with the presence of heart failure and there is a correlation between those values and the severity of both systolic and diastolic dysfunction [4-6]. Elevation of BNP often precedes heart failure symptoms and even echocardiographic changes [7]. Increased BNP levels in patients with isolated LV diastolic dysfunction can play a role in clinical stratification of this condition proportionally to its severity [8, 9]. Elevated levels of ANP and BNP are also characteristic for AF [10], and restoration of the sinus rhythm is correlated with evident decrease of natriuretic peptide levels [11, 12]. Significantly higher BNP levels are observed in individuals with AF and concomitant congestive heart failure than in patients with AF without coexisting heart failure symptoms, which can help in differentiating patients with LV dysfunction from those without it [13, 14].

In the present study we have tested the effect of sinus rhythm restitution on ANP and BNP levels in patients with proper and impaired LV diastolic function with special focus on the correlation between magnitude of changes in those levels and diastolic function.

Methods

Patients

Forty-two patients were enrolled in the study – 19 women and 23 men aged 40-75 years (mean 58.6 ± 8.2 years) with AF lasting for 1 week to 13 months (mean 11.2 ± 6.5 weeks), in whom an effective electrical cardioversion for AF was performed and sinus rhythm was maintained for at least 30 days after the procedure. The following inclusion criteria were used: proper systolic LV function with ejection fraction (EF) > 50% and with LV end-diastolic diameter index (LVEDDI) < 3.2 cm/m², without concomitant heart valve defects. Before electrical

cardioversion in all subjects proper ventricular rate control (60-90/min) and optimal blood pressure (BP) values were obtained. The exclusion criteria were: ineffectiveness of electrical cardioversion or recurrence of AF or any other cardiovascular event during the first month after cardioversion. All patients received optimal anticoagulation therapy for at least 3 weeks before and 4 weeks after cardioversion. During the first month after obtaining sinus rhythm no changes in therapy that could influence diastolic LV function had been made.

The control group consisted of 20 patients of similar age and gender but with sinus rhythm and no history of AF or other cardiovascular disorders and with no signs of impaired ventricular function assessed using echocardiography.

The protocol of the study was accepted by the local Bioethical Commission.

Protocol

Patients attended 3 visits: 24 h before cardioversion and then 24 h and 30 days after the procedure. Every appointment consisted of an interview, physical examination, ECG, echocardiography and evaluation of ANP and BNP levels. Furthermore, during the visit on the 30th day after cardioversion, cardiac diastolic function was assessed in Doppler echocardiography. The same strategy pattern was adopted for the control group.

Echocardiography

Transthoracic echocardiogram (TTE) was performed using a Siemens – Acuson Sequoia C 256 unit and 2.5-3.5 MHz second harmonic frequency probe. During the examination the following parameters were estimated: left atrium (LA) maximal dimension in parasternal long axis view (LA max), LV end-diastolic and end-systolic diameter index (LVEDDI, LVESDI), EF using Simpson's method, LV mass index (LVMI). In Doppler echocardiography the peak velocities of mitral blood flow during early diastolic filling (E-wave) and atrial contraction (A-wave) were measured along with E-wave deceleration time, isovolumetric relaxation time (IVRT), peak velocities of S-, D- and AR-wave corresponding with blood flow from the right superior pulmonary vein to the left atrium (LA). Identification of impairment in ventricular diastolic activity was based on the following criteria [8, 15, 16]:

1. Impaired LV relaxation – < 50 years of age: IVRT > 100 ms or DT > 220 ms or E/A < 1; > 50 years of age: IVRT > 105 ms or DT > 280 ms or E/A < 0.8.
2. Decreased LV compliance:
 - a) pseudonormalisation of LV filling – < 50 years of age: DT 160–220 ms and IVRT 70–100 ms and E/A 1.0–1.5 and S/D < 0.5 or ARdur > Adur o > 30 ms and VmaxAR > 0.35 m/s; > 50 years of age: DT 160–280 ms and IVRT 70–105 ms and E/A 0.8 – 1.5 and S/D < 0.5 or ARdur > Adur o > 30 ms and VmaxAR > 0.35 m/s,

b) restrictive filling pattern – DT < 160 ms and at least 2 of the following parameters: IVRT < 70 ms, E/A > 1.5, S/D < 0.5, ARdur > Adur o > 30 ms or AR > 0.35 m/s.

Evaluation of natriuretic peptide levels

Fasting blood samples for ANP and BNP level analysis were collected in the morning hours in supine position, after 30 min of rest. Blood was taken from the basilic vein to EDTA tubes with a 500 KIU/ml dose of aprotinin (Trasylol – Bayer). After that blood was centrifuged at a temperature of 4°C and the plasma was frozen at minus 70°C.

The levels of ANP and BNP were evaluated using radioimmunoassay (RIA set, Peninsula). The value of inter-series coefficient variation for ANP was 4.3% and for BNP 4.8%, while variation coefficients for different series were 6.9% and 7.7% for ANP and BNP respectively. The above values were obtained at the Department of Clinical Pharmacology at the Medical University of Silesia, Katowice.

Statistical analysis

Results are presented as mean ± SD or median. For comparison between means in unrelated pairs characterised by normal distribution and similarity in variation, Student's t-test was used. In case of asymmetric distributions, differences were measured with Wilcoxon's test. To investigate independent effects of analysed parameters, multivariate analysis was conducted. The level of statistical significance was set at $p < 0.05$.

Results

Thirty days after electrical cardioversion in patients without AF recurrence diastolic LV function was measured. Proper ventricular activity was observed in 15 patients, while the 27 remaining subjects fulfilled criteria of diastolic dysfunction – in 20 of those patients evidence of impaired relaxation was revealed and in a further 7 decreased compliance was detected (in 4 pseudonormalisation of LV filling, in 3 restrictive filling pattern). The two groups of patients mentioned above – with proper ($n = 15$) and impaired diastolic function ($n = 27$) – in clinical examination before cardioversion (during AF) were not significantly different in age, weight, body mass index (BMI), heart rate, main blood pressure and AF duration. However, the group with diastolic dysfunction contained a greater percent of women compared with the group with proper ventricular activity. Every individual with impaired relaxation had underlying hypertension history. Also, differences between subgroups in progression stage of heart failure symptoms (NYHA classification) were recorded. More severe symptoms of heart failure were observed in patients with impaired ventricular diastolic function. Although echo in groups with proper and

compromised ventricular activity showed similar LA and LV diameters and comparable EF, in the group with diastolic dysfunction more prevalent LV hypertrophy and higher values of systolic blood pressure in the right ventricle were observed.

Average plasma ANP and BNP levels estimated in patients with AF before cardioversion turned out to be significantly higher than in the control group (Table I).

Also, significant differences between ANP and BNP levels were detected at the time before cardioversion (during AF duration) between the subgroups with proper and impaired ventricular diastolic function (Table II). In subjects affected by diastolic LV dysfunction, levels of ANP and BNP were significantly higher compared to the group with proper ventricular activity.

Restoration of sinus rhythm caused a significant reduction of natriuretic peptide levels both in patients with proper LV function and individuals with impaired diastolic function (Table III). However, the actual decrease of ANP level was larger in the group suffering from ventricular diastolic dysfunction.

The BNP levels were significantly lower after cardioversion in patients with reduced LV diastolic function whereas no such changes were observed in patients with normal LV function. Changes in both ANP and BNP levels 24 h before and 30 days after cardioversion in patients with proper and impaired LV function are presented in Tables IV and V.

Table I. Mean plasma levels of ANP and BNP in patients with AF and in control group

Natriuretic peptide	AF (42 patients)	Control group (20 patients)	p
ANP [pg/ml]	233.0 ± 83.9	54.5 ± 34.7	< 0.001
BNP [pg/ml]	99.8 ± 51.2	34.0 ± 12.2	< 0.001

Table II. Mean ANP and BNP levels in patients with proper diastolic activity and with diastolic LV dysfunction 24 h before cardioversion (during AF)

LV function	ANP [pg/ml]	BNP [pg/ml]
Proper diastolic function (15 patients)	167.3 ± 70.1	49.5 ± 14.7
Diastolic dysfunction (27 patients)	298.7 ± 83.6	145.6 ± 49.6
p	< 0.001	< 0.001

Table III. Comparison of ANP and BNP levels measured 24 h before and 30 days after cardioversion

Measurement	ANP [pg/ml]	BNP [pg/ml]
24 h before	254.9 ± 79.9	113.6 ± 49.1
30 days after	153.2 ± 67.9	61.9 ± 25.1
p	< 0.001	< 0.001

Table IV. Comparison of ANP levels measured 24 h before and 30 days after cardioversion in patients with proper and impaired diastolic LV function

Parameter	Proper diastolic function of LV (n = 10)	Diastolic dysfunction (n = 20)
ANP [pg/ml] 24 h before	167.3 ± 70.1	298.7 ± 83.6
ANP [pg/ml] 30 days after	97.9 ± 34.4	185.8 ± 91.4
p	0.012	< 0.001
Decrease of ANP level [pg/ml]	64.4 ± 71.8	111.2 ± 93.9
Decrease of ANP level [%]	38	37
p	0.014	< 0.001

Table V. Comparison of BNP levels measured 24 h before and 30 days after cardioversion in patients with proper and impaired diastolic LV function

Parameter	Proper diastolic function of LV (n = 10)	Diastolic dysfunction (n = 20)
BNP [pg/ml] 24 h before	49.5 ± 14.7	145.6 ± 49.6
BNP [pg/ml] 30 days after	38.1 ± 10.8	75.9 ± 31.9
p	NS	< 0.001
Decrease of BNP level [pg/ml]	11.4 ± 16.7	67.5 ± 36.0
Decrease of BNP level [%]	23	46
p	NS	< 0.001

Abbreviations: BNP – B-type natriuretic peptide, EC – electrical cardioversion, LV – left ventricle, SD – standard deviation

Discussion

Our study showed that restoration of sinus rhythm was correlated with a significant decrease of ANP levels in measurement performed 24 h after cardioversion ($p < 0.001$). The next measurement of ANP level was made 30 days after cardioversion in patients maintaining sinus rhythm and obtained values did not show any significant change. These results are compatible with other authors' findings with respect to ANP levels in patients with sustained AF and after sinus rhythm restitution [10-12]. Many studies have unequivocally shown that AF provokes a considerable increase of plasma ANP level. Furthermore, its enhancement is unrelated to atrial dimension and capacity, LV function and concomitant cardiovascular diseases [12]. It seems that haemodynamic changes occurring during AF, volume overload, increase of atrial blood pressure and rising tension of atrial walls are the principal causes of enhanced ANP secretion associated with arrhythmia.

After restoration of sinus rhythm the ANP level drops steeply. The vast majority of authors have reported almost twofold ANP reduction after cardioversion [12, 17]. In patients with AF, sinus rhythm restitution accounts for restoration of proper atrial systolic activity and regular ventricular rhythm. The number of atrial depolarisations falls along with heart rate. The return of atrial systolic activity and efficient atrial blood evacuation leads to reduction of atrial blood pressure and muscle tone. Those changes are probably the primary cause of ANP level

reduction following effective cardioversion. In our study the ANP level, although significantly reduced after cardioversion, was still significantly higher than in control. This can be explained by the existence of diastolic dysfunction in most patients with AF history, documented by Doppler echocardiography (30 days after cardioversion in 64% of the patients in sinus rhythm diastolic ventricular dysfunction was found). This explanation may be supported by the insignificant difference of ANP levels between patients with AF and no diastolic dysfunction after sinus rhythm restoration and the control group and also by the marked difference between individuals with diastolic LV dysfunction and the control group.

The evaluation of changes in BNP levels after effective cardioversion also revealed a significant, approximately two-fold reduction assessed 24 h and 30 days after sinus rhythm restoration. The lack of significant changes in size of cardiac chambers and EF indicates that those factors did not affect BNP secretion.

The reasons for increased BNP secretion have not been fully determined. Most likely the rise of BNP level is associated primarily with elevation of diastolic blood pressure in LV as a result of ventricular filling disturbance and decreased stroke volume due to AF. Recently, new mechanisms of BNP increase were proposed by studies revealing enhancement of atrial BNP secretion during AF. In an original study by Inoue et al. [18] blood samples were collected from patients with AF during cardiac catheterisation from aorta, great cardiac vein and coronary sinus. In individuals suffering from AF the BNP

level was significantly higher in the coronary sinus than in the great cardiac vein, whereas in the control group the results were similar, which indicated that the atria are the main source of BNP. After effective cardioversion BNP level in blood from the coronary sinus was significantly reduced, reaching values registered in the control group. The increased secretion of BNP by the atria during AF has also been confirmed by other authors [18, 19]. According to a recently proposed theory, the atria could be the main source of BNP in patients with AF and without concomitant ventricular dysfunction.

The reduction of BNP level after effective cardioversion has also been confirmed by other investigators [13, 14]. Jourdain et al. [13] observed that in a group of 40 patients with AF and proper ventricular rate control and without left ventricular dysfunction, the BNP level after effective cardioversion dropped from 61.4 pg/ml to 23.5 pg/ml ($p < 0.002$).

Our data also suggested that, as was observed in the case of ANP, in patients remaining in sinus rhythm after cardioversion BNP level was significantly higher than in the control group. However, the comparison between AF patients with proper LV function and the control group showed no significant difference (38.1 vs. 34.0 pg/ml). Similar results were obtained by Ohta et al. [14], who observed BNP level reduction to 62.5 pg/ml in a group of patients with AF and LV dysfunction who underwent effective cardioversion, while in a group with AF but without LV impairment the BNP level after cardioversion was 30.3 pg/ml and was similar to the value recorded during AF.

The results presented above indicate that the magnitude of ANP and BNP levels' reduction after sinus rhythm restitution is different between subgroups with proper and impaired diastolic LV function. In the case of ANP this reduction is not as significant – although the actual decrease of ANP level in pg/ml is much larger in the subgroup with ventricular dysfunction than in patients without this condition, the magnitude of this reduction measured in percent is similar for both subgroups (Table IV). On the other hand, in the case of BNP in the subgroup with ventricular diastolic dysfunction the return of sinus rhythm was significantly associated with BNP reduction, whereas in individuals with proper ventricular function BNP decrease was insignificant (Table V). This findings may indicate that lone AF in patients with proper ventricular function and under optimal rate control, which was obtained in all subjects before natriuretic peptide level measurement, was associated predominantly with increase of ANP level (although less significant than in patients with concomitant ventricular dysfunction), while secretion of BNP was not affected as much. Meanwhile, the elevation of BNP level during AF in patients with diastolic heart failure would confirm the fact that AF causes

more severe haemodynamic dysregulation in patients with coexisting ventricular diastolic dysfunction. Impaired relaxation is due to the fact that the left atrium plays a key role in retaining proper stroke volume. Atrial fibrillation leads to loss of atrial systolic activity and that in turn, along with complete dysregularity of cardiac rhythm, significantly impairs ventricular filling – both in early- and end-diastole. As a result of these disturbances, the stroke volume decreases and diastolic blood pressure rises in both the LV and left atrium, which is associated with enhanced secretion of natriuretic peptides. Clinical observations suggest that patients suffering from diseases associated with impaired diastolic LV function (hypertension, coronary heart disease, diabetes, hypertrophic cardiomyopathy) demonstrate lower AF tolerance. In these patients sinus rhythm restitution is almost in every case associated with significant improvement of physical efficiency and reduction of symptoms. The results of large studies such as PIAF, AFFIRM, RACE, and HOT-CAFE, which compared different strategies of rate and rhythm control, have provoked heated discussions on how to treat AF [20-23]. There is still no agreement in answering the question in which patients with recurrent AF restitution of sinus rhythm is associated with the greatest benefit. Lower tolerance of arrhythmia in subjects with diastolic ventricular dysfunction and the data presented above may point to patients with diastolic dysfunction, especially impaired relaxation, as the group that could benefit most from maintaining sinus rhythm.

Study limitations

The small number of patients should be considered as an important limitation. For pragmatic reasons diastolic LV function could not be measured in echo during AF, and therefore it had to be estimated 30 days after restoration of sinus rhythm, i.e. after haemodynamic atrial stabilisation. Although changes in diastolic function usually take place very slowly and no cardiovascular events or therapeutic modifications affecting diastolic activity were registered during 30 days after cardioversion, complete exclusion of changes in ventricular diastolic function at that time is impossible. For diastolic function estimation the non-invasive method of Doppler echocardiography was used which, although most popular, unlike invasive methods has some limitations.

Conclusions

1. Natriuretic peptide levels in patients with AF after sinus rhythm restoration show a correlation with diastolic function of the left ventricle.
2. The return of sinus rhythm is associated with greater reduction of natriuretic peptide levels, especially BNP, in patients with impaired rather than preserved ventricular diastolic function.

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Wpływ czynności rozkurczowej lewej komory na zmianę stężenia peptydów natriuretycznych po kardiowersji u chorych z migotaniem przedsionków

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Streszczenie

Wstęp: Czynność rozkurczowa lewej komory (LK) ma istotny wpływ na zaburzenia hemodynamiczne związane z migotaniem przedsionków (ang. *atrial fibrillation*, AF). Peptydy natriuretyczne (ANP i BNP), biochemiczne wskaźniki czynności serca, mogą być pomocne w ocenie tych zaburzeń.

Cel: Ocena wpływu przywrócenia rytmu zatokowego na zmianę stężenia ANP i BNP u chorych z prawidłową i upośledzoną czynnością rozkurczową LK.

Metody: Do badania włączono 42 chorych (19 kobiet, 23 mężczyzn) z przetrwałym AF, z prawidłową czynnością skurczową LK, u których przeprowadzono kardiowersję elektryczną (KE) i rytm zatokowy utrzymywał się przez co najmniej 30 dni. W 30. dobie u chorych bez nawrotu AF oceniono metodą echokardiografii dopplerowskiej czynność rozkurczową LK. Przeprowadzono badanie kliniczne, EKG, badanie echokardiograficzne i oznaczano osoczowe stężenia ANP i BNP przed KE oraz 24 godz. i 30 dni po KE.

Wyniki: W 30. dobie od kardiowersji u 15 badanych stwierdzono prawidłową czynność rozkurczową LK, a u 27 – cechy upośledzonej relaksacji LK (20 chorych) lub upośledzonej podatności LK (7 chorych). W całej grupie badanej w czasie AF średnie stężenie ANP wynosiło $254,9 \pm 79,9$ pg/ml, a BNP $113,6 \pm 49,1$ pg/ml. Po przywróceniu rytmu zatokowego nastąpił znamienny spadek stężenia peptydów. Stopień obniżenia stężenia ANP i BNP zależał od czynności rozkurczowej LK. W podgrupie chorych z upośledzoną czynnością rozkurczową LK obserwowano spadek stężenia ANP po kardiowersji o $111,2 \pm 93,9$ pg/ml, tj. o 37% ($p < 0,001$), a BNP o $67,5 \pm 36,0$ pg/ml, czyli o 46% ($p < 0,001$). U chorych z prawidłową czynnością rozkurczową LK powrót rytmu zatokowego wpłynął tylko na zmianę stężenia ANP i nie miał istotnego wpływu na średnie stężenie BNP. Średni spadek ANP w tej podgrupie wyniósł $64,4 \pm 71,8$ pg/ml, tj. 38%, a BNP $11,4 \pm 16,7$ pg/ml, tj. 23% (NS).

Wnioski: Zmiany stężeń peptydów natriuretycznych po przywróceniu rytmu zatokowego u chorych z AF zależą od czynności rozkurczowej LK. Przywrócenie rytmu zatokowego powoduje większe obniżenie stężenia peptydów natriuretycznych, zwłaszcza BNP, u chorych z zaburzeniami czynności rozkurczowej LK w porównaniu z chorymi z prawidłową czynnością rozkurczową, co może świadczyć o poprawie wydolności serca w tej grupie.

Słowa kluczowe: peptydy natriuretyczne, dysfunkcja rozkurczowa, migotanie przedsionków

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