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Natriuretic peptides in patients with atrial fibrillation

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Abstract

Background: *The aim of the study was to evaluate plasma natriuretic peptides (NPs): atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations in patients with paroxysmal, persistent and permanent atrial fibrillation (AF).*

Methods and results: *The study groups consisted of 23 patients with paroxysmal AF, 42 patients with permanent AF and 77 patients with persistent AF with normal left ventricular function. The mean ANP level was increased in AF patients in the paroxysmal, persistent and permanent groups: 249 ± 88.3 pg/mL; 258 ± 89.7 pg/mL; 208 ± 76.7 pg/mL, respectively,* vs. *67 ± 21.2 pg/mL in the control subjects ($p < 0.001$). The mean BNP level was increased in AF patients in the paroxysmal, persistent and permanent groups: 99.6 ± 29.8 pg/mL; 82.3 ± ± 33 pg/mL; 95.6 ± 46.4 pg/mL, respectively,* vs. *37.5 ± 13 pg/mL in the control group. Multivariate logistic regression analysis revealed a positive correlation between ANP levels, maximal left atrial volume, heart rate and New York Heart Association (NYHA) classification, in the persistent AF patients. A positive correlation between plasma BNP levels and heart failure stage according to NYHA classification in this group was found. Baseline ANP concentrations were positively correlated with baseline BNP concentrations in AF patients.*

Conclusions: *Plasma NPs levels are increased in patients with paroxysmal, persistent and permanent AF and normal left ventricle function, and positively correlated with left atrial volume, heart rate and heart failure stage according to NYHA classification. Neurohormonal assessment does not distinguish the type of arrhythmia.* (Cardiol J 2008; 15: 525–529)

Key words: atrial fibrillation, natriuretic peptides

Introduction

Atrial fibrillation (AF), because of its clinical importance, which lies in the associated morbidity, mortality, economic impact on society and the lack of satisfactory management approaches, is the subject of active clinical and research efforts. The studies on neurohormonal remodeling in patients with AF are becoming increasingly important. The results might influence the management of these patients. Natriuretic peptides (NPs) have been shown to be very powerful prognostic markers in epidemiological and clinical trials in heart failure, acute coronary syndromes and pulmonary diseases or in the general population [1]. The two most promising NPs to measure in these regards are atrial

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natriuretic peptide (ANP) and brain natriuretic peptide (BNP) or their amino (N–) terminal tails [2].

The aim of the study was to evaluate plasma NPs: ANP and BNP concentrations in consecutive patients with paroxysmal, persistent and permanent AF admitted to the Cardiology Department, compared to subjects with sinus rhythm.

Methods

A prospective study enrolled consecutive subjects aged 40–75 years, with paroxysmal AF with duration < 48 hours, persistent with duration time > 48 hours and ≤ 12 months or permanent AF; with underlying hypertension, coronary artery disease or lone AF, with normal left ventricular function [ejection fraction (EF) ≥ 50%], between April 2002 and January 2004. The control group comprised of 20 subjects with similar concomitant diseases but with normal sinus rhythm without history of AF. The reference value of plasma NP levels was obtained from 21 healthy adult volunteers. Exclusion criteria were: congenital heart disease, rheumatic valve disease, uncontrolled hypertension, uncontrolled ventricular rate (≥ 100 beats/min), symptoms of heart failure > II according to New York Heart Association (NYHA) classification, considerable dilatation of heart cavities (left atrial anteroposterior dimension > 60 mm, left ventricle end-diastolic diameter > 65 mm, and/or left ventricular end-systolic diameter > 45 mm), EF of left ventricle in echocardiography < 50%, acute coronary syndrome within 6 weeks, renal, liver or respiratory failure or malignancy. Blood samples for ANP and BNP assessment were obtained from the antecubital vein with the patient in the supine position after a resting period of 30 min. Mean and maximum heart rate were assessed from 24-hour ECG monitoring. All specimens were collected in tubes containing EDTA (ethylenediaminetetraacetic acid) 1.5 g/L, and a protease inhibitor aprotinin (Traskolan, Jelfa, Jelenia Góra, Poland) 500 KIU/mL. The plasma was separated by centrifugation (at 2500 rpm) for 20 min at 4°C and stored at –70°C until measurement. The plasma concentrations of ANP and BNP were measured by radioimmunoassay methods (Peninsula Laboratories Inc., San Carlos, CA, USA). Values of ANP and BNP were expressed as pg/mL. The intra- and interassay coefficients of variation were, for ANP: 7.1% and 11.1%, and for BNP: 5.6% and 9.0%, consecutively. Data are given as mean ± standard deviation in cases of normal distribution, whereas median values with ranges are given for non-normally distributed variables. The clinical characteristics of the 3 patient groups were compared using the χ^2 test for categorical variables, and the unpaired *t* test for continuous variables. In cases of non-normally distributed variables, differences were tested using Wilcoxon's 2-sample test. Multivariate logistic regression analysis was performed to find correlations between plasma NP levels and some clinical and echocardiographic parameters. Statistical significance was defined as $p < 0.05$. All analyses were performed using the Statistical Analysis System program (SAS Institute, Cary, NC) version 8.2.

The study was explained to each patient and written consent was obtained. The study protocol was approved by the Local Ethical Committee.

Results

Twenty-three patients with paroxysmal AF, 42 patients with permanent AF and 77 patients with persistent AF were examined. The characteristics of the study groups are presented in Table 1. The mean baseline plasma ANP level in healthy volunteers (12 male, 9 female), aged 56 ± 10 years, was 29.7 ± 7.7 pg/mL with 95% confidence interval (CI, 21.17; 33.16 pg/mL), and BNP level was 21.6 ± ± 5.2 pg/mL with 95% CI (19.56; 24.63 pg/mL). The mean ANP level was increased in AF patients in the paroxysmal, persistent and permanent groups: 249 ± ± 88.3 pg/mL; 258 ± 89.7 pg/mL; 208 ± 76.7 pg/mL, respectively, *vs*. 67 ± 21.2 pg/mL in the control group ($p < 0.001$) (Fig. 1). A trend was found for lower levels of ANP in the permanent group compared with the persistent AF group. The mean BNP level was increased in AF patients in the paroxysmal, persistent and permanent groups: 99.6 ± ± 29.8 pg/mL; 82.3 ± 33 pg/mL; 95.6 ± 46.4 pg/mL, respectively, *vs*. 37.5 ± 13 pg/mL in the control group ($p < 0.001$) (Fig. 2). Multivariate logistic regression analysis revealed a positive correlation between ANP levels and maximal left atrial volume (LP_{vol}) ($p = 0.0001$), maximal heart rate (HR_{max}) ($p = 0.0036$) and symptoms of heart failure according to NYHA classification ($p < 0.0001$) in the persistent AF patients (Table 2). A regression function for plasma ANP was calculated as follows: ANP = –259.8 + + 1.43 × LP_{vol} + 81.45 × NYHA class + 2.17 × × HR_{max}.

The model of linear regression was statistically significant for $r^2 = 0.55$ ($r = \sqrt{r^2}$), $p < 0.0001$. A positive correlation between plasma BNP levels and heart failure stage according to NYHA classification in the AF patients was found ($p < 0.0001$) (Table 2). A regression function for plasma ANP was

Table 1. Baseline characteristics and natriuretic peptide concentrations in study groups (mean ± SD).

Data	Paroxysmal AF (n = 23)	Persistent AF (n = 77)	Permanent AF (n = 42)	Control group (n = 20)	p##
Age (years)	57.6 ± 10.5	59.8 ± 9.27	64.3 ± 7.7	61.8 ± 8.1	NS (0.077)
Gender: male/female (%)	15/8 (65)	52/25 (68)	27/15 (64)	13/7 (65)	NS
Duration of AF (hours, days, months) median/range	14 (2–48)*	101 (2–392)**	46,7 (11–66)***		
Predominant cardiac diagnosis					
Coronary artery disease (%)	6 (26)	16 (21)	11 (26)	7 (35)	NS# (0.22)
History of hypertension (%)	11 (48)	51 (66)	26 (62)	13 (65)	NS#
No heart disease (lone AF) (%)	6 (26)	10 (13)	5 (12)	–	NS#
Heart rate mean [beats/min]	90.1 ± 8.5	77.2 ± 9	81 ± 8.1	71 ± 7	< 0.001[1]
Systolic blood pressure [mm Hg)]	110 ± 15	123 ± 16	131 ± 15	129 ± 15	< 0.001[2]
Heart failure according to NYHA class (%)					NS# (0.31)
I	8 (35)	23 (30)	12 (60)	12 (60)	
II	15 (65)	42 (54)	8 (40)	8 (40)	
No symptoms of heart failure (%)	–	12 (16)	–	–	
Echocardiographic findings					
Size of left atrium antero-posterior [mm]	46.8 ± 3.7	46.6 ± 4	47.5 ± 5.3	45.2 ± 2.7	NS (0.2)
Left atrial volume [mL]	87.1 ± 22.5	88.2 ± 20	110.0 ± 35.6	78.3 ± 11.6	< 0.0001[3]
LVEDD [mm]	49.8 ± 5.7	50.8 ± 6	52.3 ± 5.8	51.7 ± 3.5	NS (0.3)
LVESD [mm]	34.1 ± 5.6	35.2 ± 6	36.4 ± 6.9	32.4 ± 3	NS (0.09)
LVEF (%)	60.3 ± 7	58.1 ± 6	56.1 ± 6.9	61.8 ± 3	0.003[4]
Baseline ANP [pg/mL]	249.0 ± 88.3	257.7 ± 89.7	207.5 ± 76.7	67 ± 21.2	< 0.001[5]
Baseline BNP [pg/mL]	99.6 ± 29.8	82,3 ± 33	95.6 ± 46.4	37.5 ± 13	< 0.001[6]

AF — atrial fibrillation; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; ANP — atrial natriuretic peptide; BNP — brain natriuretic peptide; *hours; **days; ***months; #groups were compared with the χ^2 test; ##The clinical characteristics of the two patient groups were compared with the unpaired *t* test but comparison of 4 groups was performed using analysis of variance; [1]Significant differences were noticed between persistent, permanent AF or control group and paroxysmal AF group; [2]Significant differences were noticed between all groups except persistent and permanent AF; [3]Significant differences were noticed between the permanent AF group and the other groups; [4]Significant differences were noticed between permanent and paroxysmal AF, and between permanent AF and control group; [5]Significant differences were noticed between the control group and patients of paroxysmal, persistent and permanent AF groups; [6]Significant differences were noticed between the control group and patients of paroxysmal, persistent and permanent AF groups

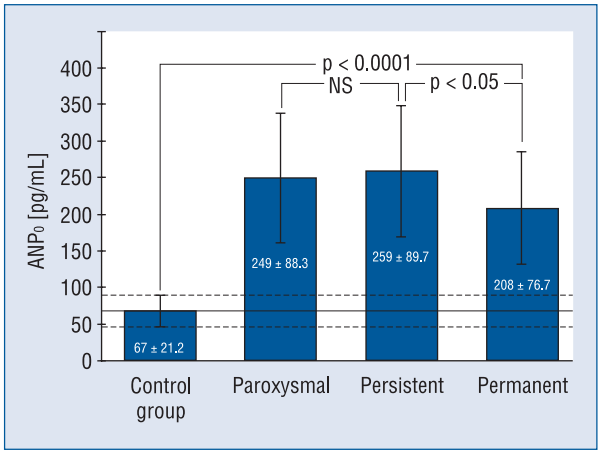

Figure 1. Plasma atrial natriuretic peptide (ANP) levels in study groups and in the control group.

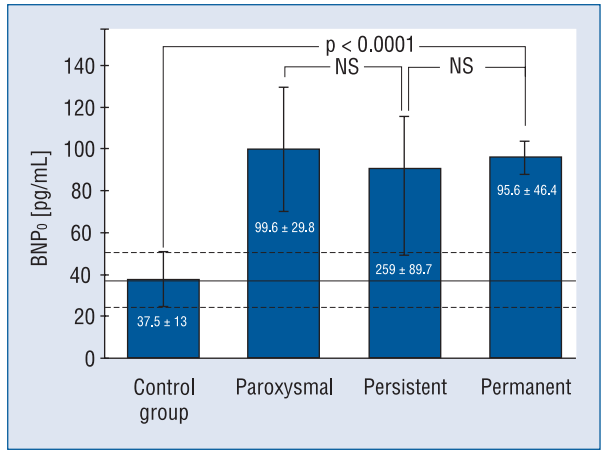

Figure 2. Plasma brain natriuretic peptide (BNP) levels in study groups and in the control group.

Table 2. The comparison of plasma ANP and BNP levels in study groups depending on symptoms of heart failure according to NYHA classification (mean ±SD).

Study group	Plasma ANP levels [pg/mL]				Plasma BNP levels [pg/mL]			
	No symptoms	I NYHA	II NYHA	p	No symptoms	I NYHA	II NYHA	p
Paroxysmal AF		209 ± 95	270 ± 80	NS (0.12)		68 ± 10	116 ± 22	< 0.0001
Persistent AF	149 ± 41	227 ± 74	305 ± 72	< 0.0001[1]	41 ± 8	64 ± 8	104 ± 28	< 0,0001[2]
Permanent AF	110 ± 23	196 ± 63	244 ± 73	0.0007[3]	49 ± 11	93 ± 43	111 ± 47	0.0228[4]
Control group		66 ± 20	68 ± 24	NS (0.87)		29 ± 3	50 ± 12	0.0032

AF — atrial fibrillation; NYHA — New York Heart Association; ANP — atrial natriuretic peptide; BNP — brain natriuretic peptide; *The plasma ANP and BNP levels of the two patient groups were compared with the unpaired *t* test but comparison of 3 groups was performed using analysis of variance; [1]Significant differences were noticed between all groups; [2]Significant differences were noticed between all groups; [3]Significant differences were noticed between the group without symptoms of heart failure and groups in classes I and II of heart failure according to NYHA classification; [4]Significant differences were noticed between the group without symptoms of heart failure and groups in class II of heart failure according to NYHA classification

calculated as follows: BNP = 36.12 + 33.25 × × NYHA class.

The model of linear regression was statistically significant for $r^2 = 0.56$ and $p < 0.001$. Plasma ANP concentrations were positively correlated with baseline BNP concentrations in all AF groups with coefficient Pearson linear correlation in paroxysmal AF $\rho = 0.65$ ($p = 0.008$), in persistent AF $\rho = 0.59$ ($p < 0.0001$), and in permanent AF $\rho = 0.43$ ($p = 0.0007$).

Discussion

In our study we demonstrated that AF in patients with normal ventricular function influences NP secretion as much in paroxysmal and persistent arrhythmia as in permanent types of arrhythmia. In our previous studies we proved the increase of ANP in persistent AF and BNP in paroxysmal type of arrhythmia [3, 4]. This is the first study to evaluate both plasma ANP and BNP peptides in paroxysmal, persistent and permanent AF patients with normal left ventricle function. The general function of NP is to modulate cardiac preload and afterload by their effect on water and electrocyte balance and cardiovascular growth. NPs also have vascular smooth muscle relaxing actions [5, 6]. The expression of both ANP and BNP is modulated by many triggers, such as wall stress, intracavity pressure loading of the circulation, and increases in atrium and ventricle dimensions in conditions of chronic pressure or volume overload. The plasma NP levels are known to be indicators of left ventricle dysfunction. The NP measurements have been used in the diagnosis of heart failure, being positively correlated to the severity of heart disease according to NYHA classification. However, the role of NP in patients with AF and preserved cardiac function has not been well determined. In the study both ANP and BNP levels were positively correlated with NYHA class in patients with persistent and permanent AF. Although ventricles were supposed to be the main source of BNP, the biochemical evidence supports a predominantly atrial source of NPs [5]. We found a positive correlation between plasma ANP concentration and left atrial volume and heart rate. The growing frequency of atrial depolarization influences the increase in the peptide concentrations during AF. It has been documented that rapid heart rate stimulates ANP release regardless of cardiac wall tension. In addition, released ANP can be stored in the cardiomyocyte granules localised in pacemaker and conduction system cells [7]. The increases in ANP and BNP secretion may be related to the sympathetic nervous system, as well as to the renin-angiotensin-aldosterone system. In the study, a close relation was observed between atrial volumes and ANP concentrations. We reported that plasma ANP release after successful cardioversion might be due to the recovery of left atrial mechanical function [8]. It confirms hypotheses that the recovery of atrial mechanical function plays a role in ANP secretion. We previously also showed that prolonged duration of AF and NP activation leads to exhaustion of the NP regulatory system, and that a decrease in the secretion reserve of atrial cardiomyocytes, documented during exercise testing, predicts cardioversion failure or AF recurrence [9, 10]. It seems that ANP in AF is a protective but time-limited system due to inherent destructive time-dependent structural and functional effects of AF. It is still under debate whether BNP is independently influenced by AF. In Rossi et al's study BNP, unlike ANP, was not affected by the presence of AF in patients with left ventricular dysfunction, organic mitral regurgitation or lone AF [11]. Unlike the

Rossi study, other authors demonstrated that AF affects BNP secretion in patients with persistent and paroxysmal types of arrhythmia and with normal left ventricular function [12–14]. The presence of AF should be taken into consideration when interpreting plasma NP concentrations. The prognostic implication of increased BNP concentrations in patients with AF seems to be different from enhanced response of ANP to increased workload. In a prospective study of a community of 3346 subjects without heart failure, NP was associated with the risk of AF (values > 80th percentile were associated with a doubling of other risks) after adjustment for traditional risk factors [15]. Further studies are required to determine the exact prognostic value of NP assays in patients with such highly heterogeneous conditions as AF and to validate the findings discussed above.

Conclusions

Plasma NP levels are increased in patients with paroxysmal, persistent and permanent AF and normal left ventricle function, and positively correlated with left atrial volume, heart rate and heart failure stage according to NYHA classification. The neurohormonal assessment does not distinguish the type of arrhythmia.

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The authors do not report any conflict of interest regarding this work.

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