Level of natriuretic peptide Determines outcome in atrial fibrillation

Qi-xian Zeng MD, Ming-fen Wei MD, Wei Zhang MD PhD, Yun Zhang MD PhD, Jing-quan Zhong MD PhD.

1 Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Health, Jinan, China; Department of Cardiology, Qilu Hospital, Shandong University, Jinan, China. 2 Shandong Communication Hospital, Jinan, China.

Abstract

Background: Natriuretic peptide (NP) is high in atrial fibrillation (AF) and may decrease after cardioversion to sinus rhythm and the levels of atrial NP (ANP) and brain NP (BNP) in different types of AF and whether ANP and BNP have predictive values for relapsed AF have not been determined.

Purpose: We aimed to examine the levels of ANP and BNP in AF to determine their roles in different types of AF, including a predictive value in relapsed AF.

Methods and Results: ANP and BNP were measured in 100 consecutive patients with AF and without heart dysfunction at baseline and in 20 controls. All patients had higher levels than controls (p<0.01). After cardioversion treatment with antiarrhythmic therapy, 40 patients failed to cardioversion successfully and still showed AF, whereas 60 patients were successful. ANP and BNP levels decreased significantly after cardioversion (163.55±54.27 pg/ml vs. 200.20±55.63 pg/ml; 124.15±43.00 pg/ml vs. 161.99±48.04 pg/ml, for ANP and BNP respectively, both p<0.0001). 18 of the 60 successfully cardioverted patients had AF recurred within 24 hours, who were then excluded from 500-day follow-up and the remaining 42 patients were enrolled. During 500-day follow-up period, AF relapsed in 16 patients. Comparing with the 42 patients, the 16 patients showed higher concentrations of ANP (187.72±32.79 pg/ml vs. 138.42±30.65 pg/ml, p<0.0001). Besides, both ANP and BNP were significantly higher in the relapsed patients than those remained SR during follow-up (153.38±29.61 pg/ml vs. 129.21±27.98 pg/ml for ANP, p=0.01 and 147.41±25.95 pg/ml vs. 121.87±20.53 pg/ml for BNP, p=0.001). The area under the receiver-operating characteristic curve was 0.799 for BNP and 0.706 for ANP in predicting a relapse of AF. Using the BNP optimized cut-off level of 138 pg/ml, relapsed AF can be predicted with relatively acceptable accuracy. Conclusions: ANP and BNP decrease significantly after cardioversion in patients with AF, and both can be useful predictors of relapsed AF.

Key Words: Atrial fibrillation; Cardioversion; ANP; BNP; relapse of atrial fibrillation.
Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias, the prevalence in the general populations is estimated to be 0.4% and increases with age.\textsuperscript{1,2} The risk of stroke and heart failure is associated with AF,\textsuperscript{3,4} and even more, AF can be an independent risk factor for death in people aged 55 to 64.\textsuperscript{5}

Atrial natriuretic peptide (ANP) is synthesized and secreted mainly in the atrium.\textsuperscript{6} During AF, atrium enlargement and atrial pressure increase are associated with elevated plasma concentration of ANP,\textsuperscript{7,8} which may decrease greatly with a return to sinus rhythm (SR)\textsuperscript{9} and this indicates its active role in AF. Brain NP (BNP), once described as an indicator of ventricular function,\textsuperscript{10-13} has drawn much attention recently in terms of AF.\textsuperscript{7, 8, 10} Although these two peptides may share some common physiological actions, including natriuresis, vasodilatation, and modulation of central and peripheral baroreflexes,\textsuperscript{14} their main origins are different, which suggests different roles in AF. In this study, we aimed to examine the levels of ANP and BNP in AF to determine whether they play a comparable role in different types of AF, including a possible predictive value in relapsed AF.

Material and Methods

Study population

The study enrolled 100 consecutive patients with AF, including paroxysmal AF (lasting < 7 days) and persistent AF (lasting ≥7 days) from our institution. The enrollment criteria were (1) clinical symptoms of AF such as palpitation and tiredness and AF revealed by 12-lead electrocardiography and (2) possible association of well-controlled mild to moderate hypertension or stable coronary heart disease. All patients underwent X-ray examination and echocardiogram to exclude severe heart dysfunction or structural heart diseases such as rheumatic heart disease or dilated cardiomyopathy, and according to the New York Heart Association (NYHA) functional classification; diabetes mellitus; hyperthyroidism; cerebrovascular disease; renal dysfunction or any other systemic diseases were also excluded. All patients were given antiarrhythmic drugs (propranolol or amiodarone) to control or eliminate AF, as well as an anticoagulant warfarin or aspirin if contradic- tive to warfarin to manage the potential hypercoagulating status, maintaining the international normalized ratio between 1.6 and 2.2. Patients received an electrocardiographic monitor during hospitalization to determine if they returned to SR (successful cardioversion group) or not (permanent AF; permAF group). Successful cardioversion group was defined as patients who returned to SR; and those who maintained SR at least 24h went to SR group. If patients failed to return to SR after cardioversion attempt, they were defined as permanent AF group (permAF group). Twenty healthy people comparable to the study patients in sex and age were recruited as a control group. Patients and controls gave their informed consent to participate, and the study was approved by the ethics committees of Qilu Hospital and Shandong Communication Hospital.

Measurement of ANP and BNP

All patients underwent blood sampling before cardioversion in the morning after having fasted for 12 h and after being supine for at least 30 min; 4 ml of blood sample was drawn from the antecubital vein then distributed into 2 polyethylene tubes and mixed well with 10% EDTA 30 μl and 50 μl of aprotinins. The tubes were then centrifuged at 3,000 rpm for 15 min at 4, and plasma was stored at -70. Blood sample was obtained using the same method immediately after cardioversion within 24 h. Plasma ANP and BNP levels were measured by enzyme-linked immunosorbent assay (ELISA) with commercially available kits (BPB Biomedicals, Inc., USA), which had a sensitivity of 0.5 pg/ml for ANP and 1.0 pg/ml for BNP, and with inter- and intra-assay coefficients of variation of <6% and <13%, respectively, for ANP and <2.0% and <4.2%, respectively, for BNP. The normal reference values for plasma ANP and BNP concentrations are <120 pg/ml and <90 pg/ml, respectively.

Follow-up

Patients in the SR group who maintained SR at least 24h after cardioversion (n=42) were followed up for 500 days after discharge. During this period, patients were interviewed by telephone.
every 2 weeks or asked to come to the clinic to undergo scheduled electrocardiography every 2 weeks, when convenient. Those who complained of symptoms of AF (reAF group) or any other discomforts were told to contact their doctor as soon as possible; the exact time of onset of the relapsed AF was recorded, and patients underwent 12-lead electrocardiography to confirm the recurrence of AF and echocardiography to measure left atrial diameters. Blood samples were taken for measurement of ANP and BNP levels within 24 h after cardioversion, or at the end of the follow-up period.

Echocardiography

Transthoracic 2-D echocardiography involved use of a GE system Model 5 Color Doppler Ultrasound (PHILIPS7500, California, USA) with the changeable transducer frequency from 2.25 to 5.5 MHz, to compare the SR group and reAF group at 500-day follow-up. Left atrial diameters were measured in the left-ventricular long axial view.

Statistical analysis

Continuous values were expressed as mean±SD and compared by ANOVA with Student-Newman-Keuls test. Multiple Coxes, proportional hazard regression model was used to identify determinants associated with risk of relapsed AF with 6 variables (age, left-atrium diameter, ANP and BNP concentration before or after cardioversion). ANP and BNP levels at baseline were examined by receiver-operating characteristic curve (ROC) analysis as predictors of relapsed AF in the successful cardioversion group; the areas under the curve (AUC) from the ROC curve were calculated, and the preferred cut-off values that provided the optimal test accuracy were derived from the ROC curve. The cumulative recurrence-free rates of all patients in the successful cardioversion group during follow-up were calculated by both Kaplan Meier and life table methods. A P<0.01 was considered statistically significant, and statistical analysis involved use of SAS 9.1 (SAS Inst., Cary, NC, USA).

Results

Patient characteristics

The characteristics of patients in different AF groups at baseline are shown in [Table 1]. All 100 patients were free of heart dysfunction (NYHA Class I). Groups did not differ by age or sex. Some patients in the successful cardioversion, permAF, SR, and reAF groups may have had cardiovascular risk factors (coronary heart disease or hypertension), but groups did not significantly differ in these factors. Groups were comparable in both systolic and diastolic blood pressure and heart rate.

Comparison of ANP and BNP levels in AF groups

As compared with the control group, ANP level was higher in all patients with AF, whether in the permAF group (175.53pg/ml±33.09 pg/ml vs. 110.06 pg/ml±29.82 pg/ml, p<0.01) or successful cardioversion group (200.20 pg/ml±55.63 pg/ml vs. 110.06 pg/ml±29.82 pg/ml, p<0.01) than con-
The permAF group showed a relatively steady, high ANP concentration, which was significantly lower than that for the successful cardioversion group before cardioversion (175.53 pg/ml ± 33.09 pg/ml vs. 200.20 pg/ml ± 55.63 pg/ml, p < 0.01). However, the ANP level became comparable after cardioversion (175.53 pg/ml ± 33.09 pg/ml vs. 163.55 pg/ml ± 54.27 pg/ml, p = NS), because the concentration of ANP in the successful cardioversion group decreased significantly after cardioversion (200.20 pg/ml ± 55.63 pg/ml vs. 163.55 pg/ml ± 54.27 pg/ml, p < 0.01) [Table 2, Figure 1].

The analysis of BNP level showed almost the same characteristics as those for ANP: both the permAF and successful cardioversion group showed a higher level of BNP than the control group (158.76 pg/ml ± 33.99 pg/ml, 161.99 pg/ml ± 48.04 pg/ml vs. 1.45 pg/ml ± 22.57 pg/ml respectively, p < 0.01) before cardioversion attempt, and the cardioversion group showed a significant decline in BNP level after cardioversion (161.99 pg/ml ± 48.04 pg/ml vs. 124.15 pg/ml ± 43.00 pg/ml, p < 0.01). However, the BNP level was similar in the permAF and successful cardioversion groups before cardioversion (158.76 pg/ml ± 33.99 pg/ml vs. 161.99 pg/ml ± 48.04 pg/ml, p = NS) but differed significantly after cardioversion (158.76 pg/ml ± 33.99 pg/ml vs. 124.15 pg/ml ± 43.00 pg/ml, p < 0.01) [Table 2, Figure 2].

Follow-up and predictors of relapsed AF

During the 500-day follow-up, 16 patients in the SR group (n=42) experienced AF relapse (reAF group) and the rest of the 26 patients remained SR at the end of follow-up period. ANP and BNP values before cardioversion were re-analyzed, and a lower concentration for both ANP and BNP in the SR group than in the reAF group (138.42 pg/ml ± 30.65 pg/ml vs. 187.72 pg/ml ± 32.79 pg/ml; 131.60 pg/ml ± 25.71 pg/ml vs. 179.56 pg/ml ± 24.43 pg/ml, respectively, both p < 0.01) had been observed [Table 3, Figure 3].

Concentrations of ANP and BNP before cardioversion, as well as patients’ age, left-atrial diameter, and concentrations of ANP and BNP after cardioversion were investigated as potential predictors of relapsed AF. Patients with (n=16) or without (n=26) recurrence of AF did not differ in age or left-atrial diameter.

Figure 1: ANP level of the control group (n=20), permAF group (n=40), and cardioversion group before and after AF reversal (n=60). AF: atrial fibrillation; permAF: permanent atrial fibrillation.

Figure 2: BNP level of the control group (n=20), permAF group (n=40), and the cardioversion group before and after AF reversal (n=60). AF: atrial fibrillation; permAF: permanent atrial fibrillation.
The ANP and BNP levels were checked within 24 hours of relapsed AF or at the end of the follow-up period if the patient remained SR. Patients with relapsed AF showed higher levels of ANP (153.38±29.61pg/ml vs. 129.21±27.98pg/ml, p=0.0112) and BNP (147.41±25.95pg/ml vs. 121.87±20.53pg/ml, p=0.0010) than those who remained SR [Table 4].

Multiple Coxes, proportional-hazard regression analysis revealed that concentration of ANP and BNP before or after cardioversion predicted relapsed AF well by univariate analysis. On stepwise multivariate analysis, only ANP and BNP before cardioversion were independent risk factors of AF recurrence: with each unit increase in BNP, the probability of relapsed AF would increase by 3.4%, when controlling for level of ANP (β=0.00335, relative risk=1.034, 95% confidence interval (CI) 1.013-1.055). With each unit increase in ANP, the probability would increase by 2.6%, when controlling for BNP (β=0.0255, relative risk=1.026, 95% CI 1.004-1.048).

The AUC of the ROC curve for baseline ANP and BNP as predictors of relapsed AF were 0.706 and 0.799, respectively [Figure 4]. From the ROC analysis, 139 pg/ml for ANP and 138 pg/ml for BNP were calculated as cut-off values of optimal test accuracy for predicting relapsed AF. Applying the optimized cut-off value for ANP revealed a sensitivity of 68.75%, a specificity of 46.15%, a positive predictive value of 44% and a negative predictive value of 70.59%. Applying the optimized cut-off value for BNP revealed a sensitivity of 68.75%, a specificity of 73.08%, a positive predictive value of 61.11% and a negative predictive value of 79.17%, which indicates that BNP is a more effective predictor of relapsed AF.

The cumulative rates of non-recurrence of AF for all patients in the successful cardioversion group during follow-up were calculated by both the Kaplan-meier and life table methods. The 100-, 200-, 300- and 500-day AF non-recurrence rates were 95.24±3.29%, 88.1±5.0%, 78.57±6.33%, 69.05±7.13% and 61.9±7.49%, respectively. With the Kaplan-meier analysis, patients with ANP<139 pg/ml or BNP<138 pg/ml retained SR more so than...
patients with higher levels (p=0.003 and p=0.002, respectively).

Discussion

Disagreement of ANP and BNP in AF

Previous studies have demonstrated that the atrium may increase its synthesis and secretion of ANP during an AF episode in association with atrial stretching,\textsuperscript{15} and the level decreases immediately after successful cardioversion.\textsuperscript{16-20} In contrast, during prolonged AF, ANP level may not be increased because of failure of the atrial productive capacity with structural atrial damage.\textsuperscript{21-22} However, most of these studies included subjects with underlying structural heart disease that may have biased the results. Patrick and associates studied level of pro-ANP in patients with AF alone and found no significant increase in pro-ANP level.\textsuperscript{23} Since pro-ANP and active ANP are released equally, we measured ANP level among different AF groups after AF. Although both the permAF and successful cardioversion groups showed elevated levels of ANP at baseline comparing with controls, the successful cardioversion group showed a higher ANP level than the permAF group before cardioversion, which sustained a steady but relatively moderate range of ANP even after cardioversion. Van Den Berg and colleagues ascribed a sustained level of ANP to an impaired ability of the atria to produce ANP because of degenerative changes\textsuperscript{21}; however, unlike the authors’ patients, none of our patients had congestive heart failure. So we cannot conclude that our findings of low ANP level in the permAF group are due to degenerative atrial change resulting in lower ANP secretion. ANP level seemed more vulnerable to the fluctuation of heart rhythm, specifically, the shift from normal to abnormal or the reverse, so that when the rhythm remained steady, even in AF, a relatively low level would be obtained.

The level of ANP in AF remains controversial, as does the level of BNP. Rossi reported that BNP was not independently associated with AF and was strongly determined by left-ventricular dysfunction, for which it was an independent marker.\textsuperscript{24} However, Nakamura\textsuperscript{25} and other researchers\textsuperscript{26} showed BNP level elevated in AF patients. Nevertheless, when AF is restored to SR, BNP showing a significant decrease has gained wide attention\textsuperscript{27-29} However, all of these study cohorts featured cardiac conditions associated with heart failure, which have been confirmed to be related to elevated BNP\textsuperscript{30-32} that would inevitably affect AF itself. All patients in the present study had AF alone. So in contrast to ANP level, BNP level did not differ between the permAF and successful cardioversion group at baseline, which agrees with 2 previous findings implicating diverse reactions in the two NPs in AF.\textsuperscript{23, 33} BNP may have much to do with AF itself or may be more coincidental with AF but can be an useful indicator of AF, whereas ANP represents the atrium status well; it can be an useful indicator of different types of AF and its severity. Further investigation of AF alone will help clarify the exact relations of the NPs with AF and explore their roles in this process.

Predictive value of ANP and BNP

The values of NPs in predicting relapse of AF are debated. Researchers have found NPs to be predictors of relapsed AF.\textsuperscript{34-35} A 1-year follow-up study of 71 AF patients with mild heart failure who then underwent direct-current cardioversion concluded that a high level of BNP together with a low level of ANP before cardioversion were risk factors of relapsed AF in patients with congestive heart failure.\textsuperscript{36} As well, poor response of ANP after exercise was a risk factor of relapsed AF after direct cardioversion.\textsuperscript{37} However, in all types of AF, as well as paroxysmal AF, the level of BNP might not assess severity or probability to relapse well.\textsuperscript{38} The diversity in findings suggests that AF has diverse intrinsic properties, so prediction is difficult. In the present study, concentrations of ANP and BNP in patients with AF alone were both significantly higher in the reAF group than in the SR group before or after cardioversion. In applying the optimized cut-off value of 138 pg/ml, the measurement of BNP provided a sensitivity of 68.75% and a specificity of 73.08% in predicting relapse of AF, which were specific than those for ANP; from Kaplan-Meier analysis, in patients with a BNP<138 pg/ml, the SR sustained rate would be higher than patients with higher BNP (p =0.002).

In conclusion, this study has revealed that the concentrations of ANP and BNP rose markedly during the onset of AF and then decreased after cardioversion but not to baseline levels. The level of ANP and BNP before and after cardioversion
can predict the outcome of AF; a level above the cut-off value may help to confirm the probability of relapsed AF.

Clinical implication

AF is a threatening disease, with mortality 2 times higher in AF patients than those with SR. It is also a costly disease, in terms of not only money but also quality of life. The earlier the atrium returns to SR the better the benefit. With the simple measurements of ANP and BNP and determination of their relationship at the first cardioversion, we may assess the severity of AF and the status of the atrium. Furthermore, applying a cut-off value of BNP may help distinguish AF that could be refractory to antiarrhythmic drug therapy and help in considering early direct-current cardioversion or ablation therapy.

Study limitations

AF is associated well with age: its prevalence and severity are increased in elderly people. Therefore, assessments of ANP and BNP should be viewed in terms of age categories. In our study, patients’ ages were in a relatively small range, which may not represent all types of AF and thus prevents generalization of results to a wider population. However, the age range in the present study was typical for AF, and the results may still help in understanding the relation between NPs and AF and their roles in predicting relapsed AF. As well, our study has the limitation of any small case-series study; the reAF group especially contained only 16 patients. Thus, the results need further investigation in a larger cohort of patients for definitive conclusions.

Acknowledgements

This study was supported by a grant from National Basic Research Program of China (973 Program, 2007CB512001) and Sponsored by NSFC (30871039), SRF for ROSC, SEM.

References