Plasma renin activity and pro-B-type natriuretic peptide levels in different atrial fibrillation types

Farklı atriyal fibrilasyon türlerinde plazma renin aktivitesi ve pro-B-tipi natriüretik peptit düzeyleri

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Abstract

Objective: Renin-angiotensin system may be activated during atrial fibrillation (AF). Our aim was to evaluate plasma renin activity (PRA) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with different AF types who had normal left ventricular (LV) systolic function.

Methods: This cross-sectional study included 97 patients with recent (≤7 days), persistent (7 days to 12 months) and permanent AF (>12 months), and age- and sex-matched 30 controls with sinus rhythm. Plasma levels of PRA and NT-pro-BNP were measured and presented as median (25^{th}-75^{th} percentiles). Echocardiographic examination was performed in all population. Variance and logistic regression analyses were also used for multiple comparisons and independent predictors, respectively.

Results: Median NT-proBNP levels were higher in overall patients with AF than in controls [114 (63-165) vs 50 (38-58) pg/ml, p<0.001), but PRA level was comparable in both groups. Similarly, NT-proBNP levels were also higher in all subtypes of AF compared with controls (p<0.05). In addition, there was a significant difference in NT-proBNP level among recent, persistent and permanent AF subtypes (p=0.001). This difference mainly derived from the recent AF subtypes. Whereas PRA level was similar in all AF subtypes and controls. Age was an independent predictor of PRA level ≥1.9 ng/ml/hour (OR=1.1, 95% CI 1.01-1.23, p=0.03). With NT-proBNP level ≥52 pg/ml, independent predictors were age (OR=1.1, 95% CI 1.01-1.19, p=0.02), presence of persistent and/or permanent AF (OR=6.8, 95% CI 1.03-45.7, p=0.04) and left atrial dimension (OR=1.2, 95% CI 1.03-1.36, p=0.02).

Conclusion: Plasma NT-proBNP levels can be associated with AF and its subtypes in patients with normal LV systolic function, whereas there was no association between PRA levels and AF. *(Anadolu Kardiyol Derg 2010; 10: 317-22)*

Key words: Plasma renin activity, B-type natriuretic peptide, atrial fibrillation, logistic regression analysis

Özet

Amaç: Atriyal fibrilasyon (AF) sırasında renin-anjiyotensin sistemi (RAS) aktif olabilir. Amacımız, sol ventrikül sistolik fonksiyonu normal olan farklı AF hastalarında, plazma renin aktivitesi (PRA) ve N-terminal pro-B-tipi natriüretik peptit (NT-proBNP) düzeylerini değerlendirmektir.

Yöntemler: Bu kesitsel çalışmaya, yeni (≤7 gün), persistan (7 gün ile 12 ay) ve kalıcı AF'si (>12 ay) olan 97 hasta alındı. Yaş ve cinsiyeti benzer sinüs ritimli 30 sağlıklı birey kontrol grubunu oluşturdu. Plazma PRA ve NT-pro-BNP düzeyleri ölçüldü (mediyan, 25th - 75th persantil). Tüm popülasyona ekokardiyografi yapıldı. Standart testlere ek olarak, çoklu karşılaştırmalar için varyans analizi ve bağımsız prediktörler için lojistik regresyon analizi kullanıldı.

Bulgular: Tüm AF grubunun ortanca NT-proBNP düzeyi, kontrol grubundan daha yüksekti [114 (63-165)'e 50 (38-58) pg/ml, p<0.001), fakat PRA düzeyi benzerdi. Benzer olarak, kontrol grubuna kıyasla, tüm AF alt-gruplarında da NT-proBNP düzeyleri daha yüksekti (p=0.001). Bu fark, başlıca yeni AF'den kaynaklandı. Oysa PRA düzeyi, tüm AF alt-gruplarında ve kontrol grubunda benzerdi. Yüksek PRA (≥1.9 ng/ml/saat) için yaş (OR=1.1, %95GA 1.01 - 1.23, p=0.03) bağımsız prediktördü. N-terminal-proBNP ≥52 pg/ml için bağımsız prediktörler ise yaş (OR=1.1, %95GA 1.01 - 1.19, p=0.02), persistan ve/veya kalıcı AF varlığı (OR=6.8, %95GA 1.03 - 45.7, p=0.04) ve sol atriyum çapı (OR=1.2, %95GA 1.03-1.36, p=0.02) idi.

Sonuç: Sol ventrikül sistolik fonksiyonu normal hastalarda, NT-proBNP düzeyleri hem AF hem de onun alt-türleriyle ilişkili olabilir. Fakat PRA düzeyleri ile AF arasında ilişki yoktu. *(Anadolu Kardiyol Derg 2010; 10: 317-22)*

Anahtar kelimeler: Plazma renin aktivitesi, B-tipi natriüretik peptit, atriyal fibrilasyon, lojistik regresyon analizi

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Introduction

Despite promising advances, treatment of atrial fibrillation (AF) is far from optimal since available drugs fail to prevent recurrences of AF effectively after successful cardioversion. Thus, current research activities target different pathogenetic mechanisms and a substrate of AF (1).

Renin-angiotensin system (RAS) can play an important role in the pathophysiology of AF, and seems to be one of the popular mechanisms (1-8). Previous studies have showed the changes in atrial expression/activity of angiotensin converting-enzyme (ACE) (3) and angiotensin II receptors (6, 7) in persistent AF patients with normal left ventricular (LV) function. Accordingly, RAS contributes to atrial electrical and structural remodeling in the AF setting (2-8). In animal model, rapid atrial pacing has been reported to elevate plasma renin activity (PRA) (8). In a recent study, however, rapid atrial depolarization has reduced the expression of renin in cellular and animal model of AF (2). There is no human study investigating the impact of AF on PRA in the literature. However, there is indirect evidence that inhibition of renin-angiotensin system (RAS) with ACE inhibitors or angiotensin receptor blockers provides a significant benefit in AF patients with heart failure or hypertension (1).

Although N-terminal pro-B-type natriuretic peptide (NT-proBNP) is mainly secreted by LV myocardium, it can also be produced from the atrial tissue (9). Previous studies have reported that NT-proBNP levels can be associated with AF in patients with normal LV systolic function (10-18). These studies included the patients with paroxysmal, persistent or chronic AF. In addition, angiotensin II may induce the secretion of NT-proBNP or BNP (19). Up to now, plasma NT-proBNP levels have not been compared systematically in different AF types.

Therefore, we investigated the levels of PRA and NT-proBNP in patients with different AF categories who had no heart failure.

Methods

Patients

This cross-sectional study included consecutively 97 patients with AF and age-and sex-matched 30 controls with sinus rhythm (SR). Detailed medical history, physical examination, routine biochemical testing were performed in addition to a 12-lead electrocardiogram (ECG). The presence of coronary artery disease, hypertension or valvular disease was considered as structural heart disease. The protocol of this study was approved by the University's Ethics committee and an informed consent was provided from each patient.

Exclusion criteria were as follows; acute coronary syndromes, presence of heart failure, severe valvular heart disease (regurgitation >2+ or stenosis >moderate), congenital heart disease, hypertrophic cardiomyopathy, thyroid dysfunction, renal failure (serum creatinine >170 mmol/L), chronic inflammatory diseases, hepatic dysfunction, malignancies, LV ejection fraction (EF) <50% and use of beta-blockers, ACE inhibitors, angiotensin receptor blockers or diuretics.

The duration of AF was determined by the patient's description of a well-defined and abrupt onset of palpitations with subsequent ECG evidence of AF at the time of presentation. Continuous ECG monitoring was not performed. Based on the arrhythmia duration, AF was categorized as recent (≤7days), persistent (7 days to 12 months) and permanent (>12 months).

Blood sampling and assays

Blood samples were drawn from the ante-cubital vein during AF after patients had rested in the horizontal position for 30 min. Samples were centrifuged and plasmas were stored at -20°C. The PRA was measured by determining angiotensin-I produced from endogenous renin substrate after incubation of plasma for 1 h at 37°C. This was accomplished by radioimmunoassay using commercial Angiotensin-I kit (Immunotech, Prague, Czech Republic). Normal range of PRA was 0.5-1.9 ng/mL/hour. Plasma level of NT-proBNP was measured by using an electrochemiluminiscence immunoassay on an Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany).

Echocardiography

All study population undergone transthoracic echocardiographic examination (Vingmed System 5, GE Healthcare). Measurements were averaged for 3 cardiac cycles in subjects with SR and for 6 cardiac cycles in patients with AF. The LVEF was measured using modified Simpson's rule. The LV systolic and diastolic diameters, as well as left atrial dimension were conventionally measured using M-Mode echocardiography. Valvular functions were evaluated with Doppler echocardiography.

Statistical analysis

All statistical analysis were performed using SPSS 11.0 program (SPSS Inc., Chicago, Il, USA). Continuous variables were defined as mean ± standard deviation. Plasma renin activity and NT-proBNP were presented median (25^{th}-75^{th} percentiles). Continuous variables were analyzed with Student's t-test or Mann-Whitney U test and categorical variables were analyzed using Chi-square test or Fisher's exact test. Multiple comparisons were performed by one-way analysis of variance (ANOVA) with Bonferroni test, Pearson Chi-square test and Kruskal-Wallis test. For NT-proBNP, a cut-value of 52 pg/ml predicted presence of AF with 84% sensitivity and 70% specificity by receiver operating characteristic analysis. For PRA, upper limit of normal value was used for univariate and multiple logistic regression tests. Univariate analysis were performed to examine potential confounders of PRA ≥1.9 ng/mL/hour and NT-proBNP ≥52 pg/ml and then all identified univariate variables of $p<0.15$ were entered into the multiple logistic regression analysis. Thereafter, odds ratios (OR) and 95% confidence intervals (CI)

were calculated. The confounders for high PRA were age, presence of AF, heart rate, thickness of LV septum and posterior wall. For higher NT-proBNP level, they were age, all AF subtypes, structural disease, heart rate, diastolic blood pressure, left atrial size, LVEF, septal and posterior wall thickness. A p value <0.05 was considered to be statistically significant.

Results

Atrial fibrillation patients versus controls

Patients with AF had a higher prevalence of structural heart disease, cardiac medications, and higher heart rate, greater left atrium and ventricle compared with controls (p<0.05 for all) (Table 1). In addition, they had much thicker LV (p<0.05).

The median NT-proBNP level was significantly higher in AF patients than controls (114 vs 50 pg/ml, p<0.001), whereas, PRA level was similar in both groups (0.96 vs 0.75 ng/ml/h, p=0.19, Table 1).

Table 1. Clinical, echocardiographic and laboratory characteristics of AF patients and controls

Variables	Controls (n=30)	All AF groups (n=97)	p**
Age, years	60.1±7.4	62.4±8.1	0.17
Male / Female, n	14/16	50/47	0.68
SHD, n	0	74	<0.001
Coronary disease, n	0	14	0.04
Hypertension, n	0	30	<0.001
Valvular disease, n	0	39	<0.001
Calcium antagonists, n	0	69	<0.001
Digoxin, n	0	11	0.06
Nitrates, n	0	4	0.57
SBP, mmHg	124±9	128±11	0.052
DBP, mmHg	74±5	77±8	0.15
Heart rate, beat/min	66±9	118±18	<0.001
LV diastolic size, mm	48.7±3.6	48.5±5.6	0.87
LV systolic size, mm	28.9±3.0	31.9±6.1	0.01
IVS, mm	9.9±0.8	11.2±1.3	<0.001
PW thickness, mm	9.6±0.8	10.6±1.2	<0.001
Ejection fraction, %	67±3	64±6	0.01
LA diameter, mm	36.0±2.4	47.1±7.5	<0.001
PRA, ng/ml/h*	0.75 (0.46-1.17)	0.96 (0.62-1.26)	0.19
PRA ≥1.9 ng/ml/h, n (%)	1 (3)	14 (14)	0.11
NT-proBNP, pg/ml*	50 (38-58)	113.6 (64.5-165.5)	<0.001
NT-proBNP ≥52 pg/ml, n (%)	12 (40)	80 (82)	<0.001

Data are presented as proportions/percentages, mean±SD and *median (25^{th}-75^{th} percentiles) values
**Student-t test for independent samples, Fisher-exact test or Mann-Whitney U test
AF- atrial fibrillation, DBP- diastolic blood pressure, IVS - interventricular septum, LA - left atrium, LV - left ventricle, NT-proBNP - N-terminal pro-B-type natriuretic peptide, PRA - plasma renin activity, PW - posterior wall thickness, SBP - systolic blood pressure, SHD - structural heart disease

Atrial fibrillation subtypes and controls

Table 2 shows clinic and echocardiographic characteristics in three AF subtypes. There were significant differences in several clinic and echocardiographic variables between each AF subtype and controls. Among three AF subtypes, there was significant difference in prevalence of structural disease, use of calcium antagonist, heart rate, EF and diameter of the left atrium and ventricle (p<0.05 for all). Persistent and permanent AF patients had a higher prevalence of structural disease and use of calcium antagonist than recent AF (p<0.01 for both). Furthermore, their heart rate was lower and left atrium and ventricle was larger compared with recent AF patients (p<0.05 for all). There was a significant difference in left atrial size between persistent and permanent AF (p=0.001), but other variables were comparable in the two groups.

Median PRA levels were comparable in all AF subtypes and controls (Table 3, Fig. 1). Whereas, NT-proBNP level was higher in each AF subtypes than in controls (p=0.001, Table 3, Fig. 1). In addition, it was also different among three AF subtypes. This difference mainly derived from recent AF (Fig. 2).

Age (p=0.13), presence of AF (p=0.12), heart rate (p=0.02), LV septum (p=0.08) and posterior wall (p=0.06) thicknesses were univariate confounders of high PRA levels. Among them, age was independently associated with high PRA levels (OR=1.1, 95% CI 1.01 - 1.23, p=0.03) (Table 4).

Univariate predictors of NT-proBNP levels ≥52 pg/ml were age (p=0.001), structural disease (p=0.001), recent AF (p=0.001), persistent AF (p=0.02), permanent AF (p=0.01), heart rate (p=0.05), diastolic blood pressure (p=0.10), left atrial diameter (p<0.001), LVEF (p=0.01), LV septum (p=0.002) and posterior wall thicknesses (p=0.001). Out of them, age (OR=1.1, 95%CI 1.01-1.19, p=0.02), non-recent AF (OR=6.8, 95%CI 1.03-45.7, p=0.04) and left atrial dimension (OR=1.2, 95%CI 1.03-1.36, p=0.02) were independent predictors (Table 4).

Discussion

In this study, NT-proBNP level was higher in AF patients without heart failure compared with controls with SR. It was also higher in persistent and permanent AF patients than recent AF patients. Moreover, it was independently associated with age, non-recent AF and left atrial diameter. However, PRA level was comparable in AF patients and controls.

The growing evidence suggests that activation of RAS may contribute to the development and recurrence of AF (1-8). Angiotensin II can induce the proliferation of fibroblasts and hypertrophy of cardiomyocytes through the mitogen-activated protein kinase pathway (2-4). Subsequently, atrial remodeling consisting of atrial hypertrophy, fibrosis and electrophysiological abnormalities may develop, which facilitates the occurrence of AF (1-8). The inhibition of RAS may prevent this remodeling in experimental models (2-5). This favorable effect has been supported indirectly by clinical studies (1). In addition, AF patients

Table 2. Clinical and echocardiographic characteristics in patients with recent, persistent and permanent AF, and controls

Variables	Controls	Recent AF		Persistent AF		Permanent AF		F/X²*	p*
	n=30	n=32	p†	n=34	p†	n=31	p†		
Age, years	60.1±7.4	60.3±9.2	0.93	64.3±7.4	0.03	62.5±7.4	0.21	2.1	0.13
Male, n	14	18	0.61	18	0.80	14	0.99	0.82	0.38
SHD, n (%)	0	14(44)	0.001	31(91)	0.001	29(93)	0.001	28	0.001
CA, n (%)	0	10(31)	0.001	28(87)	0.001	31(100)	0.001	39.4	0.001
Digoxin, n	0	2 (6)	0.49	2 (6)	0.49	5 (16)	0.05	2.31	0.31
SBP, mmHg	124±9	129±11	0.04	129±12	0.05	127±12	0.15	0.2	0.85
DBP, mmHg	74±5	77±8	0.16	78±7	0.05	76±8	0.45	0.5	0.60
HR, beats /min*	66±9	122±15**	0.001	110±16	0.001	104±14	0.001	11.6	0.001
LVed, mm*	48.7±3.6	46.1±5.0**	0.02	48.4±4.1	0.77	51.2±6.5	0.06	7.6	0.001
LVesd, mm*	28.9±3.0	29.0±4.8**	0.97	32.7±4.9	0.01	34.0±7.4	0.001	6.3	0.003
IVS, mm	9.9±0.8	11.2±1.4	0.001	11.1±1.2	0.001	11.2±1.5	0.001	0.1	0.95
PW, mm	9.6±0.8	10.5±1.2	0.001	10.6±1.0	0.001	10.7±1.3	0.001	0.4	0.71
LA size, mm*	36±2.4	40.3±5.4**	0.17	47.4±3.6	0.001	54.9±8.4***	0.001	56.2	0.001
EF, %*	67±3	66±5	0.001	62±7	0.001	62±9	0.001	4.5	0.01

Data are presented as mean±SD and proportions/percentages
*Chi-square and one-way ANOVA tests with Bonferroni posthoc comparisons:
**p<0.05 for comparison of recent AF vs persistent AF, recent AF vs permanent AF groups
***p=0.001 permanent AF vs recent AF group
†comparison of AF type groups with controls
AF- atrial fibrillation, CA- calcium antagonist, DBP- diastolic blood pressure, EF- ejection fraction, HR- heart rate, IVS - interventricular septum, LA - left atrium, LV - left ventricle, LVed - LV end-diastolic diameter, LVesd -LV end-systolic diameter, PW – posterior wall thickness, SBP - systolic blood pressure, SHD - structural heart disease

Table 3. Plasma renin activity and N-terminal pro-B-type natriuretic peptide levels in patients with recent, persistent and permanent AF

Variables	Controls	Recent AF		Persistent AF		Permanent AF		X²	p*
	n=30	n=32	p***	n=34	p***	n=31	p***		
PRA, ng/ml/h	0.75 (0.46-1.17)	0.94 (0.62-1.60)	0.25	0.94 (0.56-1.09)	0.39	1.0 (0.60-1.40)	0.21	0.22	0.90
PRA ≥1.9 ng/ml/h, n(%)	1 (3)	6 (19)	0.11	3 (9)	0.62	5 (16)	0.19	1.42	0.49
NT-proBNP pg/ml†	50 (38-58)	63 (48-91) **	0.01	123 (78-169)	0.001	138 (92-203)	0.001	22.7	0.001
NT-proBNP ≥52 pg/ml, n(%)	12 (40)	18 (56)	0.22	32 (94)	0.001	30 (97)	0.001	22.8	0.001

Data are presented as median value (25th-75th percentile) and proportions/percentages
*Pearson Chi-square, and Kruskal-Wallis tests
**p<0.001 Mann Whitney U test – comparison of recent AF vs persistent and permanent AF groups
***Mann Whitney U test – comparison of AF groups with controls
AF- atrial fibrillation, NT-proBNP - N-terminal pro-B-type natriuretic peptide, PRA - plasma renin activity

have been shown to be high atrial tissue ACE concentration as well (3). Similarly, rapid pacing has increased the concentrations of atrial angiotensin II in animal model of AF (4).

In experimental model of AF, two studies have reported divergent results with regard to renin activity or level (2, 8). The first has shown that rapid atrial pacing increased both atrial and plasma levels of PRA and atrial natriuretic peptide in a dog model (8). The other has reported that rapid atrial depolarization with pacing reduced the expression of renin in both cellular and animal model of AF while increasing expression of other components (ACE, angiotensinogen and chymase) of RAS (2). In our study, PRA levels were similar in patients with overall AF and its subtypes compared with healthy controls. We think that RAS may be activated locally in the atria of AF patients. The study of Tuinenburg et al. (20) may support this consideration. In that study, plasma levels of renin and aldosterone were comparable in heart failure patients with AF and SR.

Atrial fibrillation itself may cause LV diastolic dysfunction by some mechanisms such as myocardial energy depletion, the loss of atrial contractile function and atrioventricular synchrony

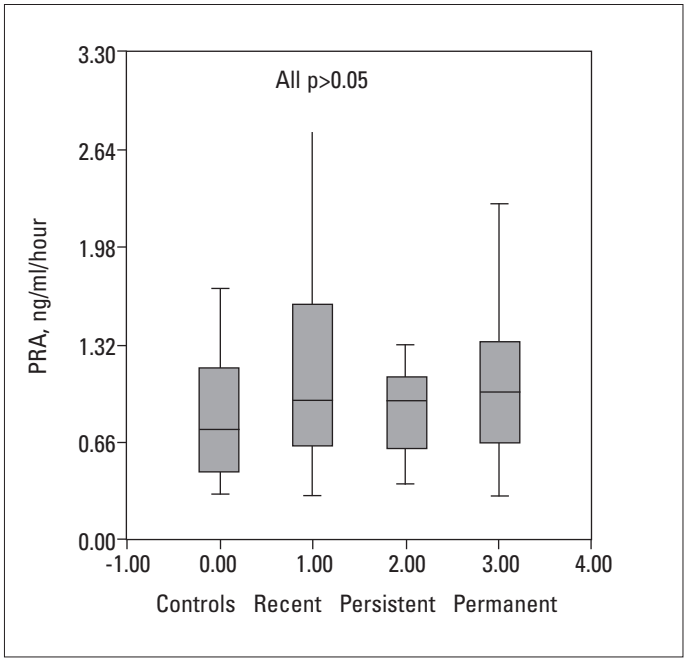

Figure 1. Plasma renin activity (PRA) levels in patients with different atrial fibrillation (AF) types, and controls with sinus rhythm. Boxes represent median and 25th to 75th percentile range and whiskers show 5th to 95th percentiles. Median PRA levels were comparable in all groups

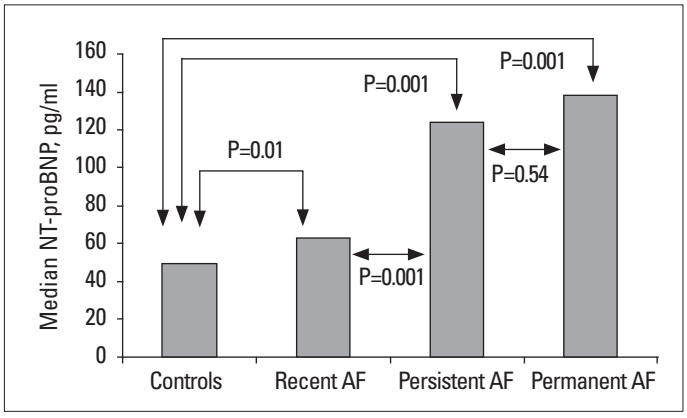

Figure 2. Comparison of N-terminal pro-B-type natriuretic (NT-proBNP) level in different atrial fibrillation (AF) categories with healthy controls with sinus rhythm

Table 4. Independent predictors associated with high PRA and NT-proBNP levels

Variables	Odds ratio	95% confidence interval	p
PRA ≥1.9 ng/ml/hour			
Age	1.1	1.01 - 1.23	0.03
NT-proBNP ≥52 pg/ml			
Age	1.1	1.01 - 1.19	0.02
Non-recent AF	6.8	1.03 - 45.7	0.04
Left atrial size	1.2	1.03 - 1.36	0.02

Multiple logistic regression analysis
AF -atrial fibrillation, NT-proBNP-N-terminal pro-B-type natriuretic peptide, PRA -plasma renin activity

(21). In this setting, atrial pressure can be elevated, which induce atrial remodeling. Atrial remodeling may facilitate the perpetuation and recurrence of AF (1-8). N-terminal-proBNP or BNP level is elevated in both LV systolic and diastolic dysfunction (14, 22). In the present study, AF patients had higher NT-proBNP levels compared with healthy subjects. Similarly, NT-proBNP level was higher in patients with persistent or permanent AF compared with those with recent AF. Therefore, elevated NT-proBNP level may reflect the high pressure in the left atrium and be an early sign of occult LV diastolic dysfunction in AF patients.

In our study, left atrial dilatation was significantly related to high NT-proBNP level as in previous studies (11, 16-22). Other independent predictors of high NT-proBNP level were age and presence of persistent or permanent AF. These findings are in accordance with the results of previous studies (11, 17, 18, 23, 24). In previous studies, structural heart disease such as hypertension and coronary artery disease were significantly associated with NT-proBNP or BNP (10, 11, 18, 23, 24). However, a similar association was not found in our study and another study (12). We think that left atrium may be enlarged due to high filling pressure and atrial remodeling in persistent or permanent AF. Thus, long-term AF will increase the level of NT-proBNP, especially in case of poor rate control of AF.

Our study has showed that NT-proBNP level was associated with non-recent AF. A similar association has been demonstrated in a recent study (17). Furthermore, Tuinenburg et al. (25) have reported that persistent AF induced the expression of proBNP in atrial tissue but paroxysmal AF did not. However, BNP levels were comparable in paroxysmal and persistent AF patients in another study (13).

Study limitations

There are several limitations to this study. Firstly, its size was small due to strict inclusion criteria. On the other hand, this situation may have given rise to selection bias. The AF population was heterogeneous, including valvular and coronary heart disease, hypertension and no structural disease. However, these structural diseases had no predictive value for high NT-proBNP and PRA levels. Angiotensin II, a marker of RAS activation was not evaluated since its assay is too difficult. Finally, detailed evaluation of LV diastolic dysfunction was not performed. Its presence may affect our results.

Conclusion

Our results show that AF and its subtypes can be associated with NT-proBNP levels in patients with normal LV systolic function. However, there was no association between AF and PRA levels.

Conflict of interest: None declared.

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