Chapter 7

Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation

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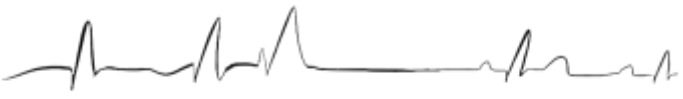

Abstract

Background: The presence of atrial fibrillation (AF) is related to increased levels of natriuretic peptides. In addition, increased natriuretic peptide levels are predictive of the development of AF. However, the role of natriuretic peptides to predict recurrence of AF after radiofrequency catheter ablation (RFCA) is controversial.

Objective: To investigate the role of natriuretic peptides to predict AF recurrence after RFCA for AF.

Methods: In 87 patients undergoing RFCA for symptomatic drug-refractory AF, pre-procedural NT-proANP and NT-proBNP plasma levels were determined. In addition, a comprehensive clinical and echocardiographic evaluation was performed at baseline. Left atrial volumes, left ventricular volumes and function (systolic and diastolic) were assessed. During a 6 months follow-up period, AF recurrence was monitored and defined as any registration of AF on ECG or an episode of AF longer than 30 seconds on 24-hour Holter monitoring. The role of natriuretic peptide plasma levels to predict AF recurrence after RFCA was studied.

Results: During follow-up, 66 patients (76%) maintained sinus rhythm (SR), whereas 21 patients (24%) had AF recurrence. Patients with AF recurrence had higher baseline natriuretic peptide levels than patients who maintained SR (NT-proANP: 3.19 nmol/L [2.55-4.28] versus 2.52 nmol/L [1.69-3.55], p=0.030; NT-proBNP: 156.4 pg/mL [64.1-345.3] versus 84.6 pg/mL [43.3-142.7], p=0.036). However, NT-proBNP was an independent predictor of AF recurrence, whereas NT-proANP was not. Moreover, NT-proBNP had an incremental value over echocardiographic characteristics to predict AF recurrence after RFCA.

Conclusion: Baseline NT-proBNP plasma level is an independent predictor of AF recurrence after RFCA.

Introduction

Radiofrequency catheter ablation (RFCA) is considered a reasonable treatment option for patients with symptomatic, drug refractory atrial fibrillation (AF).[1] However, this treatment modality is associated with a considerable recurrence rate.[2] Several parameters have been related to a high risk for AF recurrence such as age, hypertension, type of AF, left atrial (LA) size and impaired left ventricular (LV) systolic function.[3-6] These risk factors seem to either cause or reflect structural changes (i.e. structural remodeling) of the atria that promote the perpetuation of AF and, thereby, limit the efficacy of RFCA. Accordingly, pre-procedural evaluation of the extent of atrial remodeling could be used to identify patients with an increased risk of AF recurrence after RFCA. However, at an early stage of atrial remodeling, conventional imaging techniques (e.g. two-dimensional echocardiography to assess LA size) may not be sensitive enough to predict whether a patient will experience AF recurrence after RFCA. Therefore, more sensitive indicators of atrial remodeling are needed.

Natriuretic peptides are hormones released from the atria and/or ventricles in response to volume or pressure overload.[7] In patients with AF, natriuretic peptide levels are elevated.[8-10] Potentially, plasma levels of natriuretic peptides could provide insight into the presence of underlying cardiac conditions that cause structural changes to the LA and may limit the efficacy of RFCA.

The aim of this study was to investigate the prognostic role of natriuretic peptides to predict AF recurrence in patients with preserved LV systolic function undergoing RFCA for paroxysmal AF.

Methods

Patient population and evaluation

The study population included patients with drug-refractory symptomatic paroxysmal AF and preserved LV systolic function (ejection fraction >50%), who were referred for RFCA. Atrial fibrillation was classified as paroxysmal when episodes were generally self-terminating and lasted no longer than 7 days, according to the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines definitions.[11] At admission, a blood sample was obtained to measure natriuretic peptide levels and a comprehensive transthoracic echocardiography examination was performed. To minimize the effect of AF on plasma natriuretic peptide levels, only patients with paroxysmal AF who were in sinus rhythm (SR) during blood sampling were studied. After ablation, all patients were evaluated on a systematic basis (1, 3 and 6 months after RFCA) at the outpatient clinic during a 6 months follow-up period. Routine electrocardiograms (ECG) were recorded each visit and 24-hour Holter registrations were scheduled after 3 and 6 months follow-up. Importantly, all patients were encouraged to obtain an ECG registration when experiencing palpitations. During follow-up, all medications were continued for at least 3 months. Afterwards, anti-arrhythmic drugs were discontinued at the discretion of the physician. After a blanking period of 3 months, recurrence of AF was defined as any recording of AF on ECG or an episode longer than 30 s on 24-hour Holter monitoring. Accordingly, the role of baseline clinical characteristics, baseline echocardiographic characteristics and baseline natriuretic peptide levels to predict AF recurrence after RFCA was studied.

Biochemical analysis

Blood samples were obtained from the antecubital vein at admission. An ECG recording was made during sampling to determine the heart rhythm. Plasma and serum samples were stored at −80°C prior to assay. Levels of amino-terminal-pro-atrial natriuretic peptide (NT-proANP) were determined using a radioimmunoassay (ELISA, Biomedica, Vienna, Austria) which has a measurement range of 0–10 nmol/L and a detection limit of 0.05 nmol/L. Inter-assay variation was 4% and intra-assay variability was 2%. Levels of amino-terminal-pro-B-type natriuretic peptide (NT-proBNP) were measured using an automated immunoassay (Elecsys, Roche, Basel, Switzerland). The reference range was 0–400 pg/mL and the intra-assay variability was 1.8% at high concentrations of NT-proBNP (800 pg/mL) and 2.7% at low concentrations (2.1 pg/mL).

Echocardiography

Two-dimensional transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid 7, General Electric Vingmed, Milwaukee, WI, United States), equipped with a 3.5-MHz transducer at a depth of 16 cm. All patients were imaged in left lateral decubitus position. Two-dimensional and color Doppler data were obtained in parasternal (short- and long-axis) and apical (2- and 4-chamber images) views. All images were ECG-triggered and stored in cineloop format for offline analyses. Offline analyses were performed using EchoPac 108.1.5 (General Electric Medical Systems, Horten, Norway).

Maximum LA volume was obtained from the apical views by disc's method.[12] Left ventricular (LV) end-diastolic and end-systolic volumes were obtained from the apical views and LV ejection fraction was calculated according to the Simpson's method.[12] Left ventricular and atrial volumes were

indexed to body surface area. Left ventricular diastolic function was evaluated using pulsed-wave Doppler recordings of the mitral valve inflow pattern (E-wave, A-wave, deceleration time of the E-wave) and Doppler tissue recordings of the mitral annular motion (E'-wave). In addition, the diastolic function grade was classified as either normal, grade 1 (impaired relaxation), grade 2 (pseudonormalization) or grade 3 (restrictive filling pattern) as recommended by current guidelines.[13]

Radiofrequency catheter ablation

The ablation was aimed at creating circular lesions around the left and right pulmonary vein ostia. All patients received intravenous heparin to maintain an activated clotting time of 300-400 s. Intracardiac echocardiography was used to exclude a cardiac thrombus and to guide the transseptal puncture. A non-fluoroscopic electroanatomical mapping system with multi-slice computed tomography integration was used to guide the ablation procedure (CARTO XP™, Cartomerge™, Biosense Webster, Diamond Bar, CA, USA). Mapping and ablation was performed using a 3.5-mm quadripolar open-loop irrigated mapping/ablation catheter (7.5Fr Navistar™, Biosense Webster). Radiofrequency current was applied at 30-35 W with a maximum temperature of 45°C and an irrigation flow of 20 ml/min until a bipolar voltage of <0.1 mV was achieved, with a maximum of 60 s per point. The end-point of the procedure was PV isolation as confirmed by recording entrance block during SR or pacing in the coronary sinus.[1]

Statistical analysis

All variables were tested for a normal distribution with the Kolmogorov-Smirnov test. Normally distributed continuous variables are represented as mean ± SD and non-normally distributed continuous variables are represented

as median (25^{th} - 75^{th} percentile). Categorical variables are presented as number (percentage). Statistical comparisons for continuous variables were performed with the Student's t-test or with the Mann-Whitney U-test as appropriate. Statistical comparisons for categorical variables were performed with the Chi-square test. Univariable and multivariable Cox proportional hazard analyses were performed to investigate the relation between natriuretic peptide levels and the risk for AF recurrence after ablation. Multivariable analyses were performed using an 'enter' method. Due to the limited number of events, multivariable analyses were limited to three variables. Separate models were created to correct for known clinical determinants of natriuretic peptide levels (age and gender) and to correct for the strongest univariate predictors of AF recurrence in the present population (LA volume index and LV end-systolic volume index). The incremental prognostic value of natriuretic peptides to predict AF recurrence was studied by calculating the improvement in global Chi-square after addition of NT-proANP or NT-proBNP to the model. In addition, for each Cox regression model the c-statistic was calculated. All statistical analyses were performed with SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered statistically significant.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. No extramural funding was used to support this work.

Results

Patient characteristics

The present patient population was prospectively included from an ongoing clinical registry.[14] Out of 140 consecutive patients undergoing catheter ablation for AF, 87 patients were in SR during the baseline blood test and comprised the patient population (70 men [80%], mean age 55.0 ± 9.4 years). None of the

patients previously underwent RFCA for AF. Mean duration of AF was 65 ± 60 months and the mean number of anti-arrhythmic drugs used was 3.4 ± 1.4 per patient. Mean LA volume index was 42 ± 12 ml/m^2 and mean LV ejection fraction was 59 ± 6% as assessed by transthoracic echocardiography. The mean pre-procedural AF burden on 24-hour Holter monitoring was 8 ± 19%. None of the patients had significant valvular heart disease. The procedural end-point of PV isolation was reached in all patients. No major peri-procedural complications occurred.

Table 1. Clinical characteristics of the patient population

	All patients (n=87)	Non-recurrence (n=66)	Recurrence (n=21)	p-value*
Age (years)	55 ± 9	55 ± 9	56 ± 11	0.78
Male gender, n (%)	70 (80)	52 (79)	18 (86)	0.49
Body Surface Area (m^2)	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.93
Duration of AF (months)	65 ± 60	62 ± 59	73 ± 64	0.48
History of cardioversion, n (%)	53 (61)	38 (58)	15 (71)	0.32
History of persistent AF, n (%)	9 (10)	6 (9)	3 (14)	0.50
Number of failed AAD	3.4 ± 1.4	3.3 ± 1.3	3.7 ± 1.4	0.27
Pre-procedural AF burden (%)	8 ± 19	8 ± 18	9 ± 20	0.68
Hypertension, n (%)	37 (43)	27 (41)	10 (48)	0.70
Medication:				
• *β-Blocker, n (%)*	21 (25)	14 (21)	7 (33)	0.27
• *Ca-channel blocker, n (%)*	16 (18)	11 (17)	5 (24	0.46
• *Class IC AAD, n (%)*	30 (35)	24 (36)	6 (29)	0.49
• *Class III AAD, n (%)*	51 (60)	38 (58)	13 (62)	0.78
• *ACE inhibitor/ATII, n (%)*	40 (46)	28 (42)	12 (57)	0.23

AAD = Anti-arrhythmic drugs, AF = atrial fibrillation, ECV = electrocardioversion, FU = follow-up, LA = left atrium, SR = sinus rhythm. * p-value recurrence versus non-recurrence.

After a mean follow-up of 6.6 ± 3.0 months, 66 patients (76%) maintained stable SR (non-recurrence group), whereas 21 patients (24%) had recurrent AF (recurrence group). Baseline clinical and echocardiographic characteristics are reported in Tables 1 and 2, respectively. In the recurrence group significantly larger LV volumes were noted compared to the non-

recurrence group (LV end-diastolic volume index: 54 ± 9 ml/m^2 versus 48 ± 12 ml/m^2, p=0.037; and LV end-systolic volume index: 23 ± 4 ml/m^2 versus 20 ± 6 ml/m^2, p=0.027). Importantly, LV systolic function was similar in both groups (LV ejection fraction: 57 ± 4% versus 59 ± 6%, p=0.32). Furthermore, in the recurrence group a significantly higher E-wave velocity (0.75 ± 0.23 m/s versus 0.65 ± 0.14 m/s, p=0.021), higher E/E'-ratio (10.1 ± 4.0 versus 8.4 ± 3.1, p=0.049) and higher LA volume index (47 ± 12 ml/m^2 versus 41 ± 11 ml/m^2, p=0.043) were observed. However, no differences in diastolic function grade were found between both groups, with the majority of the patients showing normal LV filling pattern (Table 2).

Table 2. Echocardiographic characteristics of the patient population

	All patients (n=87)	Non-recurrence (n=66)	Recurrence (n=21)	p-value*
LA maximum volume index (ml/m^2)	42 ± 12	41 ± 11	47 ± 12	0.043
LV end-diastolic volume index (ml/m^2)	50 ± 11	48 ± 12	54 ± 9	0.037
LV end-systolic volume index (ml/m^2)	21 ± 5	20 ± 6	23 ± 4	0.027
LV ejection fraction (%)	59 ± 6	59 ± 6	57 ± 4	0.32
Pulsed wave Doppler:				
• E-wave (m/s)	0.68 ± 0.17	0.65 ± 0.14	0.75 ± 0.23	0.021
• A-wave (m/s)	0.61 ± 0.16	0.61 ± 0.17	0.61 ± 0.12	0.97
• E/A-ratio	1.14 ± 0.35	1.12 ± 0.34	1.21 ± 0.40	0.36
• Deceleration time (s)	252 ± 74	247 ± 70	267 ± 88	0.30
Doppler tissue imaging:				
• E'-wave (cm/s)	8.3 ± 2.5	8.5 ± 2.6	7.8 ± 2.1	0.30
• E/E'-ratio	8.8 ± 3.4	8.4 ± 3.1	10.1 ± 4.0	0.049
Diastolic function grade:				
• Normal, n (%)	55 (63)	43 (65)	12 (57)	0.51
• Gr 1: Impaired relaxation, n (%)	32 (37)	23 (35)	9 (43)	
• Gr 2: Pseudo-normalization, n (%)	0 (0)	0 (0)	0 (0)	
• Gr 3: Restrictive filling pattern, n (%)	0 (0)	0 (0)	0 (0)	

AF = atrial fibrillation, FU = follow-up, Gr = grade, LA = left atrium, LV = left ventricle, SR = sinus rhythm. * p-value recurrence versus non-recurrence.

Natriuretic peptides and AF recurrence after RFCA

Prior to the ablation procedure, blood samples were obtained to measure baseline NT-proANP and NT-proBNP levels. The median level of NT-proANP was 2.69 nmol/L (1.86-3.60) and the median level of NT-proBNP was 90.9 pg/mL (49.9-159.9). No relation was found between baseline NT-proANP and NT-proBNP levels and pre-procedural AF burden assessed by 24-hour Holter monitoring. Baseline NT-proANP and NT-proBNP levels were significantly higher in the recurrence group than in the non-recurrence group (NT-proANP: 3.19 nmol/L [2.55-4.28] versus 2.52 nmol/L [1.69-3.55], p=0.030; NT-proBNP: 156.4 pg/mL [64.1-345.3] versus 84.6 pg/mL [43.3-142.7], p=0.036) (Figure 1). Cox proportional hazard analyses showed that each 100 pg/mL increase in NT-proBNP level was associated with an approximately 35% increased risk for AF recurrence (unadjusted HR: 1.205, p=0.029) (Figure 2). In contrast, each nmol/L increase in NT-proANP level was not significantly associated with a higher risk for AF recurrence (unadjusted HR: 1.204, p=0.055) (Figure 2). After correction for age and gender, the prognostic value of NT-proANP to predict AF recurrence improved (HR: 1.292, p=0.029) but was lost after correction for LA size and LV size (HR: 1.213, p=0.088) (Figure 2). In contrast, NT-proBNP maintained its prognostic value to predict AF recurrence after correcting both for age and gender and for LA size and LV size (HR: 1.390, p=0.006; HR: 1.250, p=0.023, respectively) (Figure 2). Furthermore, addition of NT-proBNP to a Cox model including LA volume index and LV end-systolic volume index resulted in a significant improvement of the global Chi-square value (7.0 vs 11.7, p=0.033), illustrating the incremental value of NT-proBNP over LA size and LV size to predict AF recurrence after RFCA (Figure 3). In contrast, NT-proANP had no incremental value over LA volume index or LV end-systolic volume to predict AF recurrence after RFCA (global Chi-square 7.0 vs 9.9, p=0.11) (Figure 3). The c-statistics for each Cox model are shown in table 3.

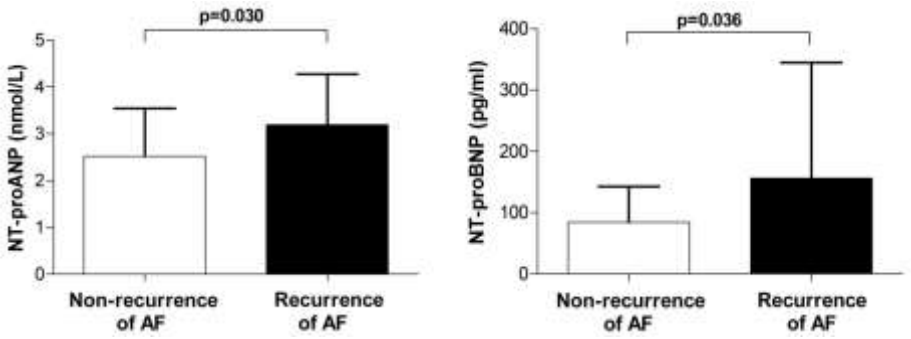

Figure 1. Baseline natriuretic peptide levels in patients with and without recurrence of atrial fibrillation (AF). Bar graphs representing median and 75th percentile of amino-terminal-pro-atrial natriuretic peptide (NT-proANP) and amino-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels measured at baseline in patients with AF recurrence and in non-recurrence patients. Baseline NT-proANP and NT-proBNP levels were significantly higher in patients with recurrence of AF during follow-up compared to non-recurrence patients.

Discussion

The present study investigated the role of natriuretic peptides to predict AF recurrence after RFCA in patients without signs of structural heart disease. The main finding was that pre-procedural NT-proBNP plasma level was an independent predictor of AF recurrence after RFCA. Importantly, NT-proBNP plasma level had an incremental value over echocardiographic parameters to predict the AF recurrence after RFCA.

Conventional echocardiography and AF recurrence after RFCA

Echocardiography is an important tool to identify patients with a high risk for AF recurrence after RFCA. In particular, LA enlargement on echocardiography is a well recognized risk factor for AF recurrence after RFCA.[4,5,15] In the present study, patients with AF recurrence had significantly larger LA than patients who maintained SR during follow-up. This finding is consistent with other studies.[4,5,15] Most likely, a large LA size reflects a high extent of atrial remodeling, which is associated with a limited efficacy of RFCA.

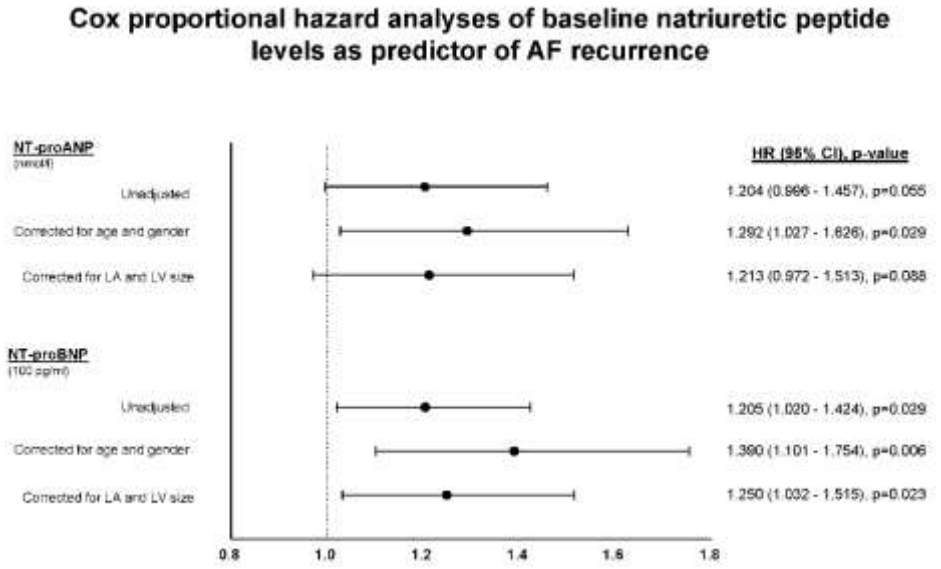

Figure 2. Cox proportional hazard analyses of baseline natriuretic peptide levels as predictor of atrial fibrillation (AF) recurrence. Hazard ratios unadjusted and corrected for age/gender and left atrial (LA) size/left ventricular (LV) size to predict AF recurrence after catheter ablation using baseline natriuretic peptide levels. Left atrial volume index and LV end-diastolic volume index were used to correct for LA and LV size, respectively. NT-proANP = amino-terminal-pro-atrial natriuretic peptide, NT-proBNP = amino-terminal-pro-B-type natriuretic peptide.

In addition to being a marker of structural LA remodeling, LA enlargement is a morphologic marker of chronic elevation in LV filling pressure (i.e. diastolic dysfunction).[16] Atrial fibrillation has been associated with LV diastolic dysfunction previously.[17] Elevated LV filling pressure may result in an elevated LA pressure and, consequentially, in LA dilatation. Accordingly, diastolic dysfunction may induce ultrastructural changes of the atria which facilitate re-entry and play an important role in the progression and perpetuation of AF.[18,19] In the present study, patients with AF recurrence had a significantly larger LA size, increased E-wave velocity and an increased E/E'-ratio, compared to patients who maintained SR. However, in the present study these diastolic function parameters were within normal range. Moreover, the

majority of patients showed a normal LV filling pattern and the prevalence of diastolic dysfunction grade 1 was similar in patients with and without AF recurrence. Therefore, at an early stage of the underlying disease, conventional echocardiography may not be sensitive enough to identify patients who will develop AF recurrence after RFCA from patients who will not. The use of more sensitive markers of cardiac dysfunction may help to improve risk stratification in patients with apparent "lone" AF and without overt structural heart disease on echocardiography.

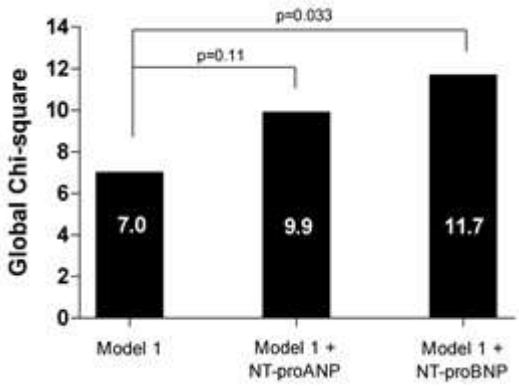

Figure 3. Incremental value of amino-terminal-pro-atrial natriuretic peptide (NT-proANP) and amino-terminal-pro-B-type natriuretic peptide (NT-proBNP) to predict atrial fibrillation (AF) recurrence after ablation. Bar graph illustrating the change in global Chi-square value by the addition of NT-proANP or NT-proBNP to a Cox proportional hazard model comprising left atrial volume index and left ventricular end-diastolic volume index (Model 1). The addition of NT-proANP to the model did not result in significant improvement of the global Chi-square. In contrast, the addition of NT-proBNP significantly improved the global Chi-square, thereby demonstrating the incremental value of NT-proBNP to predict AF recurrence after RFCA.Natriuretic peptides and AF recurrence after RFCA

The relation between natriuretic peptide levels and AF has been well recognized.[8-10,20,21] Previous studies have demonstrated that natriuretic peptide levels are elevated in patients with AF,[8-10] and that natriuretic peptides are a predictor of new-onset AF in the general population.[20,21] Nevertheless, the role of natriuretic peptides to identify patients with a high risk for AF recurrence after RFCA remains controversial. Although several studies have demonstrated the value of natriuretic peptides to predict AF recurrence after RFCA,[22,23] other

studies concluded that natriuretic peptides are merely a marker of AF burden.[24-26] However, most studies comprised a small number of patients and were performed without regard of the presence of AF during blood sampling. This is important because the presence of AF has a large impact on natriuretic peptide levels and can potentially limit its prognostic value.[8,27] To minimize this potential effect in the present study, only samples acquired during SR were analyzed. After statistical correction for known determinants of natriuretic peptide levels as well as for echocardiographic risk factors for AF recurrence, NT-proBNP was found to be a strong predictor of AF recurrence after RFCA. In contrast, NT-proANP levels were only predictive for AF recurrence after correction for age and gender. These results most likely reflect the different sensitivities of the NT-proANP and NT-proBNP release mechanisms to the primary process causing AF.[28] Furthermore, the present study demonstrated that baseline NT-proBNP had an additional value to baseline echocardiographic parameters to predict AF recurrence after RFCA. Most likely, NT-proBNP allows detection of subtle cardiac dysfunction/conditions that limit the efficacy of RFCA for AF and may not be detected by conventional echocardiography alone.

Table 3. Cox proportional hazards models

	C-statistic	95% confidence interval
Model 1	0.719	0.601-0.836
Model 1 + NT-proANP	0.763	0.661-0.864
Model 1 + NT-proBNP	0.762	0.647-0.877

Model 1: Left atrial maximum volume index + left ventricular end-diastolic volume index. NT-proANP = amino-terminal-pro-atrial natriuretic peptide, NT-proBNP = amino-terminal-pro-B-type natriuretic peptide

Clinical implications

Pre-procedural assessment of NT-proBNP in addition to echocardiography can be used to identify patients with a high risk for AF recurrence after RFCA. In

patients with paroxysmal AF and preserved LV systolic function, NT-proBNP levels may provide insight into the presence and severity of an underlying cardiac dysfunction/condition that may not be detected by echocardiography. If further validated, this information may be used during pre-procedural consultation to better inform patients about their risk for AF recurrence after RFCA. Furthermore, in patients with high NT-proBNP levels, the creation of a more extensive lesion set could be considered in order to improve the outcome of the procedure. Finally, high NT-proBNP levels should raise the electrophysiologist's suspicion on the presence of a potentially treatable underlying condition. In addition, assessment of NT-proBNP is easy and tests are widely available.

Limitations

Some limitations of the present study should be acknowledged. First, detection of AF recurrence after RFCA was based on ECG recordings acquired on a regular basis and/or 24-hour Holter registration. Importantly, patients were encouraged to obtain an ECG registration when experiencing palpitations in order to confirm AF as the cause of these complaints. Nevertheless, asymptomatic episodes may have been missed. Second, to minimize the confounding effect of heart rhythm on natriuretic peptide levels, a selected population, comprising only patients with paroxysmal AF that were in SR during pre-procedural blood sampling, has been studied. Third, the present study comprised a relatively small group of patients. Therefore only a limited number of variables could be incorporated into the multivariable analyses. To create a valid risk stratification system, the present findings need to be validated in a larger group of patients including a risk reclassification analysis. Fourth, the continuation and discontinuation of anti-arrhythmic drugs during

follow-up was at the discretion of the physician and was therefore non-standardized.

Conclusion

In patients without signs of overt structural heart disease, baseline NT-proBNP plasma level obtained during SR is an independent predictor of AF recurrence after RFCA. Plasma levels of NT-proBNP may allow detection of subtle cardiac dysfunction/conditions that may not be detected by echocardiography alone.

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