



Role of NT-pro BNP Levels as a Marker of Early and Late Recurrence in Patients Submitted to Atrial Fibrillation Ablation with Normal Ventricular Function

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Abstract: *BACKGROUND:* Levels of NT-pro BNP has diagnostic and prognostic correlation in patients with heart failure. It is also described as a possible marker of atrial myocardial disease in patients with normal ventricular function associated with atrial fibrillation (AFib). Retrospective and prospective studies have shown that their high dosage prior and few months after AF ablation may be a risk factor for recurrence. *OBJECTIVE:* Determine if in patients submitted to first AFib ablation the previous levels of NT-pro BNP and at 6 and 12 months after the procedure the modification in these levels by the restoring and maintenance of sinus rhythm can identify patients at higher risk of recurrence of atrial tachyarrhythmias. *METHODS AND RESULTS:* From June 2015 and June 2017 we sequentially began the NT-pro BNP serial dosing in patients with paroxysmal and persistent AFib with preserved ventricular function. Levels were in the previous week, 6 and 12 months after the procedure. We prospectively analyzed 73 patients submitted to first time ablation of atrial fibrillation. In pre-procedure set 33 patients had elevated concentrations. Of these 15 (45.5%) remained elevated with a 40% recurrence rate at 12-months compared to 5.5% for those which normalized the levels. On the other hand, we had 40 patients that we considered normal NT-pro BNP levels before ablation. Of these 15 (37.5%) do not had a descent of more than 50% from baseline levels had recurrence rates of 33.3% at 12 months. The remaining 25 (62.5%) who show drops > 50% of NT-pro BNP recurrence was of only 8%. Patients who had high concentrations of NT-pro BNP or who did not present a significant decrease in these levels were, respectively, 2.25 and 2.28 times more likely to present atrial arrhythmias recurrences after catheter ablation. *CONCLUSION:* Our data showed that serial levels of NT-pro BNP in patients with atrial fibrillation and normal ejection fraction might identify those at higher risk of recurrence after successful catheter ablation.

Keywords: Biomarkers, NT-pro BNP, Catheter Ablation, Atrial Fibrillation, Atrial Flutter and Recurrence

1. Introduction and Objective

Brain Natriuretic Peptide (BNP) has been identified and described since 1988 in pig brains and has structural and functional similarity to another hormone, the Atrial Natriuretic Peptide (ANP). Initially, its form of investigation was with the mature form of BNP, BNP-32, passing after the

dosage of the amino-terminal form of BNP, the NT-pro BNP [19].

Initial research has been directed at correlating high levels of the hormone as more advanced forms of heart failure because the secretion of larger quantities is in the ventricles. The main diagnostic tools for its use were heart failure, asymptomatic systolic dysfunction [16], diastolic dysfunction,

right ventricular disorders and as an etiological diagnosis of dyspnea [12]. Associated with these factors, the prognostic values and therapeutic potentials of the hormone were also documented.

In other circumstances such as AFib which is characterized primarily by electrical remodeling and atrial contractility deterioration the inappropriately rapid ventricular response, loss of the atrial contribution to the cardiac output, and atrial overloading lead to neurohormonal system activation and elevation of ANP and BNP [20] (figure 1). These levels have been demonstrated that after sinus rhythm achievement by successful current cardioversion and MAZE procedures droop to normal [15, 17].

AFib ablation with pulmonary vein isolation (PVI) for paroxysmal and persistent types has been described as a curative procedure [10]. In these cases, sequence levels of NT-pro BNP pre and post-procedure as a marker of success and consequently recurrence has not been described.

In this descriptive pilot study, we targeted to correlate the serial levels of NT-pro BNP with the success of patients with normal cardiac function who done PVI for treatment of AFib.

2. Methods

2.1. Participants and Study Settings

We prospectively analyzed between June 2015 and June 2017 73 patients were divided in two groups according to the NT-pro BNP levels into two groups denominated Group A for patients with abnormal NT-pro BNP levels and Group B for those with normal NT-pro BNP levels. These were symptomatic patients, with paroxysmal or persistent AFib with preserved left ventricular ejection fraction and who were submitted to a first-time procedure. Definition of the types of AFib was described previously elsewhere [10].

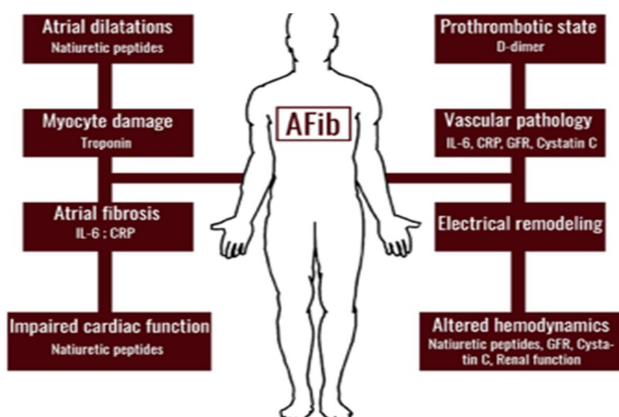


Figure 1. Atrial fibrillation and the pathophysiological changes associated with it (IL-6 Interleucin 6, CRP C Reactive Protein, GFR Growth Factor Releasing Hormone).

Protocol was collecting blood samples to dosage the levels of NT-pro BNP one week previous of the ablation, 6 and 12 months after the procedure. All patients had antiarrhythmic drugs suspended 5 half-lives before procedure, except for amiodarone that were maintained, and after 90 days

post-ablation. Recurrence was defined as clinical symptomatic atrial fibrillation, flutter or tachycardia documented by 12-lead electrocardiogram or an asymptomatic 10 minutes or more of these arrhythmias on the 24 hours Holter monitoring. Clinical and cardiovascular features as anticoagulants and antiarrhythmics drugs are described in Tables 1 and 2 respectively.

On all patients of the study we had NT-pro BNP levels at 6 months and at 12 months that we called the final recurrence (FR) rate and the normalization rate (NR), considering the patients who presented recurrence at 6 months post ablation but showed normalization of the rhythm at the final of the study.

2.2. Catheter Ablation Procedure

All patients were successfully submitted to antral isolation of the pulmonary veins [18]. Patients with previous diagnosis of atrial flutter was also treated at the end of the PVI. Procedures were performed in sinus rhythm. On the day of the procedure a total of 27 (36.98%) patients who were atrial fibrillation or flutter were submitted to electrical cardioversion. At the end of the procedure we made in all patients a challenge of 12mg of Adenosine for each of the four pulmonary veins to seek for dormant veins and vein reconnection [6, 19]. We used the Flexibility Catheter with 30 Watts of power and 30ml/min irrigation with IBI T9-1500 radiofrequency generator and the support of EnSite Velocity electroanatomic mapping, Intracardiac Echocardiography with ViewFlex catheter, all of which belongs to St Jude Medical™ (St Jude Medical / Abbott - USA) portfolio.

All patients received esophageal temperature monitoring as described in a previous study [8].

Table 1. Patients clinical features (group A and B).

| Clinical Features | Group A | Group B |
|-----------------------------------|--------------|--------------|
| Gender (male) – n% | 20 (60.6%) | 26 (65%) |
| Age years (Min/Max) | 65 (38/83) | 56 (26/70) |
| AFIB type – n (%): | | |
| Paroxysmal | 18 (54.5%) | 28 (70%) |
| Persistent | 15 (45.5%) | 12 (30%) |
| Ejection Fraction X % (Min/Max) | 61.2 (50/68) | 67.2 (62/78) |
| LA Diameter Xmm (Min/Max) | 45.2 (33/56) | 38.7 (28/49) |
| Time with AFIB X months (Min/Max) | 19.3 (11/31) | 13 (8/22) |
| Arterial Hypertension N (%) | 26 (78.8%) | 24 (60%) |
| Coronary disease N (%) | 5 (15.1%) | 6 (15%) |
| Diabetes Mellitus (DM) N % | 10 (30.3%) | 8 (20%) |
| Stroke / TIA N (%) | 4 (12.1) | 4 (10%) |
| CHADSVASC – X (Min/Max) | 2 (0 to 6) | 2 (0 to 6) |
| P Value (for all) | | 0.95 |

2.3. Informed Consent and Ethical Considerations

All patients signed the informed consent form according to the institution's standards that follow national and international patterns [4, 21]. The study was approved by the Human Research Ethics Committee of the Institution.

2.4. NT-pro BNP Levels

Blood samples for NT-pro BNP concentrations were performed with peripheral vein dosing one week prior to ablation and at 6 and 12 months after the procedure. As there are variations in the reference of normality of the biomarker that include age and sex and being the average age of the study 60 years, we adopt as normal values a limit up to 200pg / dL, as it was reference in series of other studies [14, 15]. The dosage method was of ELFA with apparatus Mini Vidas Automated Immunoassay Analyzer by bioMérieux.

Table 2. Medications used: Anticoagulants and Antiarrhythmics Drugs.

| Medications Used* - N (%) | Groups A and B (N=73) |
|---------------------------|-----------------------|
| Apixaban | 6 (8.2%) |
| Dabigatran | 40 (54.8%) |
| Rivaroxaban | 20 (27.4%) |
| Warfarin | 7 (9.6%) |
| Amiodarone | 34 (46.6%) |
| Propafenone | 30 (41%) |
| Sotalol | 9 (12.3%) |
| Beta-blockers | 18 (24.6%) |

* All medications suspended after 90 days post-procedure.

2.5. Pre-Ablation Echocardiogram

All patients underwent transesophageal echocardiography predicting the procedure. Thrombus exclusion, left atrial diameter measurements and left ventricular function through the ejection fraction were performed between 24 and 72 hours prior to ablation. Two-dimensional echocardiograms were performed in the parasternal long- and short-axis views and apical 4- and 2-chamber views. Standard two-dimensional measurements (LV end diastolic and end-systolic dimensions, ventricular septal and posterior wall thickness) were obtained with M-mode quantification. Ejection fraction was calculated by Teicholz method. For the evaluation of irregular rhythms at the time of echocardiographic study, ten consecutive cardiac cycles were recorded for the Doppler echocardiographic assessment and the results from 5 cardiac cycles, excluding the longest and shortest cardiac cycles, were averaged [13]. The patients who were on atrial fibrillation the diastolic dysfunction was not analyzed. The echocardiograms were made by GE Vivid 7 (GE Healthcare-USA) and Philips CX50 (Philips-USA).

2.6. Rhythm Monitoring

The follow-up of patients was made with electrocardiogram on hospital discharge, up to 15 days, 1, 3, 6 and 12 months after ablation. The 24-hour Holter monitoring at 6 and 12 months after the procedure.

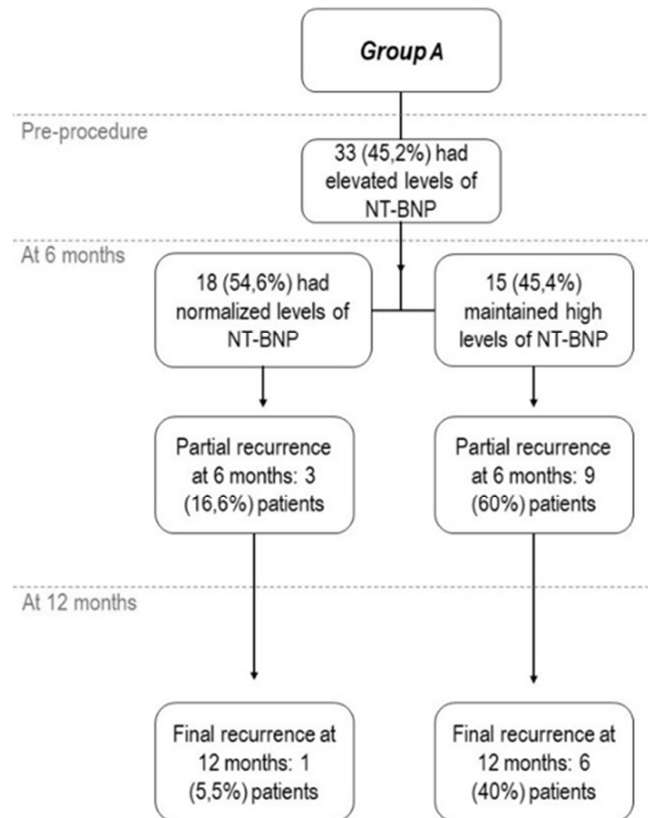


Figure 2. Group A algorithm.

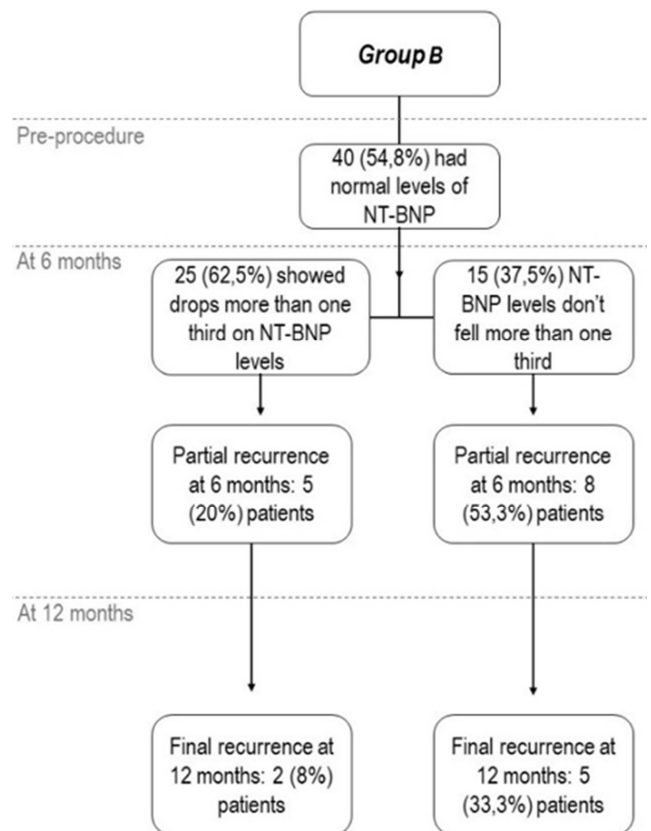


Figure 3. Group B algorithm.

Patients were encouraged to report any complaints

suggestive of arrhythmia as well as to seek out our reference service including the clinic or the Hospital for electrocardiogram performance and clinical evaluation. As all patients was submitted to ablation for having symptomatic AFib we considered recurrence if the patient had suggestive symptoms with an electrocardiogram or Holter tracings of atrial tachyarrhythmias (atrial tachycardia, atypical atrial flutter or AFib). In the 24 hours Holter monitoring when patients do not had reference of any symptom recurrence was considered with atrial tachycardia for more than 10 minutes.

3. Statistical Analysis

Statistical analysis used the t test for correlation between averages of two groups and the odds ratiotest to identify the risk of recurrence between groups considering three important factors (high level of NT-BNP, resistance in decreasing NT-BNP levels and recurrence). All tests were performed using BioEstat 5.0 statistical software.

4. Results

As described before we divide the results into two groups.

Group A consisted of 33 patients who had abnormally high levels of NT-pro BNP pre-ablation with an average of $448.2 \pm 187 \text{ pg/dl}$ since the normal level was accepted as 200 pg/dl in this study [7, 14, 15]. After the procedure on the 6 months NT-pro BNP in 18 patients presented significant drops to normal levels with reductions to average levels of $178 \pm 59 \text{ pg/dl}$ and $166 \pm 32 \text{ pg/dl}$ at 6 and 12 months. In this subgroup we documented the presence recurrences rates at 6 months and 12 months of 16.6% and 5.5% respectively. On the 15 patients who maintained high levels of NT-BNP with $352.1 \pm 104 \text{ pg/dl}$ and $279.6 \pm 55 \text{ pg/dl}$ at 6 and 12 months after ablation we saw that the recurrence rate at 6 and 12 months was 60% and 40% respectively (Figure 2). In group B, 40 patients presented normal levels with an average of $182 \pm 51 \text{ pg/dl}$ and even in this group we also observed differences between patients with higher or lower rates of atrial tachyarrhythmias after ablation. In a sub analysis, the first subgroup of 25 patients who presented a significant decrease of more than 51,65% that we called a drop in more than one-half in relation to the previous NT-pro BNP levels recurrence rates were much lower with 20% (5 patients) and 8% (2 patients) at 6 and 12 months respectively. The levels of NT-pro BNP at 6 months were $114 \pm 33 \text{ pg/dl}$ and $88 \pm 28 \text{ pg/dl}$ at 12 months. The partial recurrence was 20% and final recurrence of 8%. In the subgroup of 15 patients with falls below one-half from baseline we observed that recurrence rates of atrial arrhythmias were higher at 6 and 12 months (Figure 3). These indices were 40% and 33% for partial, 6 months, and final recurrence (FR), 12 months, respectively. The average dosages of NT-BNP were $142 \pm 39 \text{ pg/dl}$ and $130 \pm 31 \text{ pg/dl}$ at 6 and 12 months.

These findings tell us an important data. In both groups patients that do not show falls in the NT-pro BNP levels after ablation have a significant higher recurrence rate of atrial

tachyarrhythmias ($P < 0.0001$), in partial at 6 months, and final at 12 months follow-up. When we used the odds ratio test the data collected at the end of the study showed us that in the Group A patients that maintained abnormal values of the biomarker had 2.25 more chances of an atrial tachyarrhythmia when compared to those who normalized it. We also see similar results in the Group B with a 2.28 higher chance of arrhythmia recurrence for those with no significant drop after ablation.

5. Discussion

According to our best knowledge this article was the first to analyze and perform serial levels of NT-pro BNP and to evaluate its correlations with recurrence at 6 and 12 months in patients with normal ventricular function post-ablation of atrial fibrillation. In other papers the authors do not divided the patients in groups with normal and elevated levels of the biomarker a circumstance that we did in this article and which we also think that is very important since in the group of normal levels of BNP we have different behaviors since patients that had a more prominent drop have significant lower rates of recurrence.

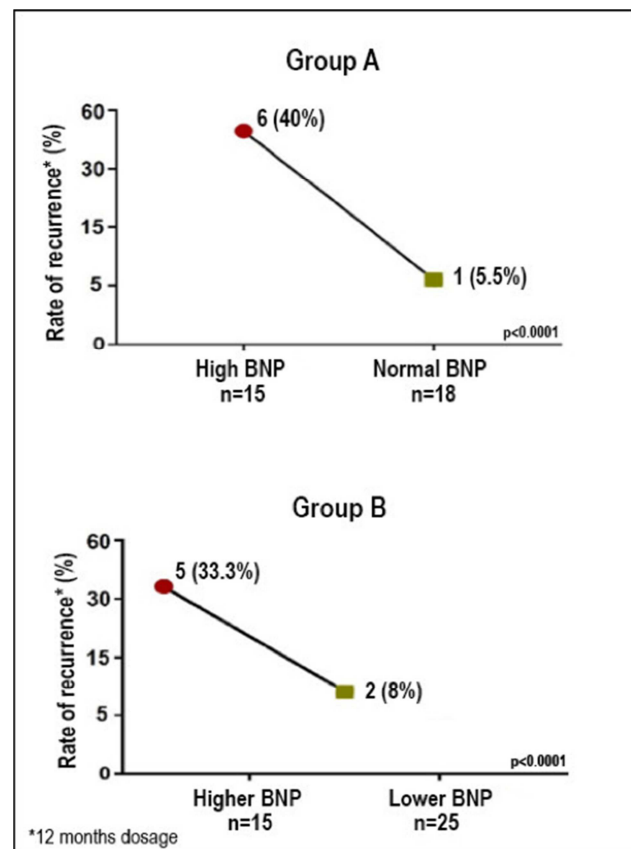


Figure 4. Final recurrence rates in Groups A and B (P value of < 0.0001 for both groups).

Previous studies published with NT-pro BNP dosages between 3- and 6-months post-procedure demonstrate that isolation of pulmonary veins effectively leads to adequate rhythm and heart rate control and as a result there are a drop to

normal levels and there is thus correlation with the success of the intervention [12]. This and other studies [1, 2, 5, 9] as well as our hypothesis, is that NT-pro BNP is a reliable marker of myocardial injury in patients with atrial fibrillation in patients without left ventricular ejection fraction reduction and that control of the ventricle heart rate would bring this hormone to normal levels.

Therefore, we believe that with restoration of sinus rhythm and its maintenance over the months NT-pro BNP levels become lower even in patients who did not present high and/or abnormal values prior to the procedure. We also made a sub analysis of the patients with normal levels of this preprocedural biomarker. We observed that when there was a decrease of more than half of these values at 6 and 12 months, we were able to identify patients with a higher or lower risk of recurrence, which may be directly related to greater or less burden of atrial tachyarrhythmias, respectively.

In our study we also observed a higher incidence of atrial tachyarrhythmias including atrial fibrillation, flutter and atrial tachycardia when we performed 24 hours Holter at 6 than at 12 months, remembering that all patients at this time were off antiarrhythmics since these medications were suspended at 3 months after ablation. This fact can be explained by a common effect that we observed in at least 30% of patients undergoing this type of intervention that another author and ourselves attribute to the local inflammatory process of radiofrequency that can last up to 3 months of the procedure. In this pilot study we can discuss if this blanking period can lasts more than 3 months and can goes at least at 6 months post-ablation since we had a significant drop in recurrence rate at the end of the study. However even considering this blanking period that could be a bias in our study our results at the end of the study are maintained with greater recurrence of arrhythmias in patients with higher levels of the biomarker studied when compared to baseline. The present study may open a discussion for an individualized and very simple way to make a practical follow-up in the post-ablation of atrial fibrillation identifying patients with a higher risk of recurrences.

Table 3. Recurrence rates in group A (patients with high NT-BNP levels). Group A1: patients maintained elevated levels of NT-BNP. Group A2: patients who normalized NT-BNP levels.

| Group A (33 patients) | Group A1 (15) | Group A2 (18) |
|-------------------------------|---------------|---------------|
| BNP LEVELS | ABNORMAL | NORMAL |
| Partial Recurrence (6 months) | 9 (60%) | 3 (16.6%) |
| Final Recurrence (12 months) | 6 (40%) | 1 (5.5%) |
| Normalization Rate | 3 (33.3%) | 2 (66.6%) |
| P VALUE | p<0.0001 | |

Table 4. Recurrence rates in group B (patients with normal NT-BNP levels). Group B1: patients maintained elevated levels of NT-BNP. Group B2: patients who normalized NT-BNP levels.

| GROUP B (40 patients) | Group B1 (15) | Group B2 (25) |
|-------------------------------|---------------|---------------|
| BNP LEVELS | DROP < 50% | DROP > 50% |
| Partial Recurrence (6 months) | 8 (53.5%) | 5 (20%) |
| Final Recurrence (12 months) | 5 (33.3%) | 2 (8%) |
| Normalization Rate | 3 (37.5%) | 3 (60%) |
| P VALUE | p<0.0001 | |

6. Study Limitations

Our study did not aim to determine if variations between atrial fibrillation types being paroxysmal or persistent could affect the outcome since previous studies had previously determined that restoration of sinus rhythm independently from the AFib type would improve NT-pro BNP levels. In addition, only 27 (37%) patients were in different rhythms of the sinus in the day of the procedure and maybe in the day of the collection of blood samples to determine NT-pro BNP levels, which contributes to higher levels of this biomarker and to the belief that this data the type of AFib did not affect our results, but the burden of the of tachyarrhythmias during the study does enhance the levels of this biomarker.

We also observed another factor that we did not relate, which was the size and volume of the left atrium, because just as the type of AFib can also be a bias in view of the possibility of changes in the levels of this biomarker. As the study was performed only in patients with preserved left ventricular function, we did not perform sub analyses in this subgroup of patients according to left atrial diameter, normal versus augmented.

We must also describe that patients with elevated levels of NT-pro BNP at 6 months could have normal or lower levels at the dosage of 12 months since our aim was not to make sequential analyses of each individual included in the trial. In addition, it should be emphasized that the expression of NT-pro BNP is higher in the ventricles and the lower myocardial mass of the atrium may be limited in the dosages of this biomarker in this type of situation and perhaps the use of NT-pro ANP results in more reliable results [2, 11].

7. Conclusion

This descriptive observational pilot study shows that serial dosages of NT-pro BNP in patients submitted to first time catheter ablation of atrial fibrillation and with normal ejection fraction identify individuals at higher risk of recurrence of atrial tachyarrhythmias at 6 and 12 months, markedly those who has high pre-ablation levels and which remains elevated after the procedure.

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