Cardiovascular Topics

Association of plasma BNP levels at different times with cardioversion success, maintenance of sinus rhythm and severity of diastolic dysfunction in patients with atrial fibrillation

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Abstract

Objective: Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults worldwide, exerting a substantial impact on health, society and healthcare economics. Despite the current management strategies involving direct-current cardioversion (DCCV) and anti-arrhythmic drug therapy, recurrence of AF remains a significant challenge. Brain natriuretic peptide (BNP), a crucial neurohormone, has been associated with AF recurrence; however, existing studies have yielded inconclusive results. Diastolic dysfunction, assessed using echocardiography, has also been implicated in AF recurrence. This study aimed to clarify the relationship between BNP levels, echocardiographic parameters and cardioversion success in patients with persistent AF.

Methods: This prospective, observational study enrolled 31 patients with persistent AF. Transthoracic (TTE) and transoesophageal echocardiography, alongside BNP measurements, were performed at various intervals: before cardioversion, 30 minutes post cardioversion and during a one-month follow up. Electrocardiography and TTE were conducted at the one-month mark, categorising patients based on diastolic dysfunction.

Results: Of the 31 patients, 28 successfully converted to sinus rhythm after DCCV. Baseline BNP levels correlated with heart rate and peak E/Em ratio. Patients with early AF recurrence had higher 30-minute BNP levels. Basal BNP levels were not found to be useful in predicting early AF recurrence, whereas BNP levels at the 30th minute after cardioversion were significantly higher in the group with AF recurrence (318 ± 39.7 vs 153 ± 11.9 pg/ml; $p = 0.05$). Patients with or without mild diastolic dysfunction showed significantly lower BNP levels than those with moderate-to-severe dysfunction.

Conclusion: The study concluded that BNP levels, measured 30 minutes after DCCV, were more indicative of maintaining sinus rhythm than baseline levels. The correlation between baseline BNP and diastolic dysfunction parameters suggests a potential combined assessment for guiding rhythm-control strategies in patients with AF.

Keywords: Atrial fibrillation (AF), cardioversion, diastolic functions, echocardiography, brain natriuretic peptide (BNP)

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Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults worldwide. AF is closely linked to considerable morbidity and mortality rates, therefore exerting a substantial impact on patients, societal health and the healthcare economy. The current estimated prevalence of AF in adults is between 2% and 4%, with a projected 2.3-fold increase due to increased life expectancy in the general population, and increased efforts to identify previously undiagnosed cases.[1]

The management of AF includes rhythm restoration or rate control, co-morbidity management, and prevention of stroke and systemic thromboembolism.[1,2] Direct-current cardioversion (DCCV) is a safe procedure that can effectively terminate AF. It has a low major complication rate of only 0.3%, including post-cardioversion stroke (0.1%), hypoxia (0.1%) and hypotension (0.1%).[3] Furthermore, it is highly successful in restoring sinus rhythm (SR) in nearly 90% of the cases.

Despite the high success rates of cardioversion, recurrence of AF remains a significant challenge. Currently, anti-arrhythmic drug therapy plays a crucial role in maintaining SR after cardioversion. Amiodarone is commonly prescribed and is considered one of the most effective anti-arrhythmia drugs.[1,4] Additionally, it is important to note that recurrence of AF is common after successful DCCV, with recurrence rates reaching as high as 40% within the first month.[5]

AF exhibits heterogeneity as a disease. The use of simple and objective parameters to identify patients at risk of relapse can greatly assist personalised treatment. The main factors associated with an increased risk of recurrence of AF are age, history of prior AF, left ventricular (LV) dysfunction, enlargement

of the left atrium, function of the left atrial appendage and hyperthyroidism.[1,6]

Brain natriuretic peptide (BNP) is a vital neurohormone produced by the ventricles in response to myocardial stretching. It serves as a key diagnostic marker for heart failure and systemic fluid overload, helping assess and manage these conditions.[7] Elevated plasma BNP levels have been observed in patients with AF compared with those in SR, even in individuals without heart failure.[8]

Several studies have shown an association between BNP level and recurrence of AF before electrical cardioversion; however, other studies have failed to show this association.[9–13] Another meta-analysis suggested that low BNP levels are associated with the maintenance of SR, and that baseline BNP levels may serve as a predictor of AF recurrence after successful electrical cardioversion.[14]

LV diastolic dysfunction may be a common factor underlying a permissive profibrillatory environment that promotes the initiation and recurrence of AF.[15,16] The assessment of diastolic function by echocardiography is critical in assessing the risk of AF recurrence after electrical cardioversion.[17] Due to previous inconclusive studies on the relationship between BNP levels in AF before cardioversion, the success of cardioversion and the maintenance of SR after cardioversion, we aimed to investigate the relationship between BNP measurements and echocardiographic parameters of diastolic dysfunction before cardioversion, and 30 minutes and 30 days after cardioversion, in association with the success of cardioversion and the maintenance of SR.

Methods

This prospective, observational study was carried out at the Department of Cardiology, Faculty of Medicine, Dokuz Eylul University, and involved a cohort of 31 patients diagnosed with persistent AF. All participants provided permission and informed consent for their involvement in the study. The study protocol was approved by the Ethics Committee of Dokuz Eylül University Faculty of Medicine.

Inclusion criteria for the study were as follows: age 18 years or older and having electrocardiography (ECG) supporting persistent AF at least seven days earlier. Exclusion criteria were: (1) paroxysmal or permanent AF, (2) patients with ejection fraction <50%, (3) those with severe valvular disease, (4) patients showing signs and puzzles of heart failure, (5) those with structural heart disease, such as hypertrophic cardiomyopathy and ventricular septal defect, (6) patients with hypo- and hyperthyroidism, (7) chronic renal failure, or (8) pregnancy.

Patients were divided into three groups based on their rhythm status after cardioversion: group 1 consisted of those who achieved successful cardioversion and SR, group 2 included patients with early recurrence of AF after cardioversion and group 3 comprised patients who failed to achieve SR with cardioversion.

All patients in this study underwent transthoracic (TTE) and transoesophageal echocardiography (TEE) using an HP Sonos 4500 device. Cardiac diameters were assessed according to the guidelines of the American Society of Echocardiography.[18] The ejection fraction was determined using M-mode echocardiography.

In the apical four-chamber view, obtained from the tip of the mitral leaflets using pulsed-wave Doppler with an angular deviation of less than 20°, the transmitral early diastolic peak flow velocity (peak E) was measured. The mitral annular motion velocity, obtained from the lateral area of the mitral annulus, was assessed using tissue Doppler imaging to derive the peak Em. Peak E/Em values were calculated to assess ventricular diastolic function. During TEE, thrombus or spontaneous echo contrast is present within the cardiac structures, particularly in the left atrial appendage. The peak flow velocity of the left atrial appendage was recorded in all patients.

DCCV was performed in all patients who had no thrombus in their cardiac structures after TEE. The procedure was performed under sedation and analgesia. A Hewlett Packard Code Master XL delivering a monophasic shock wave was used for DCCV. Prior to cardioversion, five-minute mean heart rates and initial 12-lead ECG recordings were recorded while the patients were monitored in the coronary intensive care unit. After DCCV, 12-lead ECG recordings were obtained for all the patients. All the patients were treated with unfractionated heparin before cardioversion and warfarin after cardioversion. Amiodarone was the preferred anti-arrhythmia treatment in all cases where patients were in SR.

For BNP measurement procedure, a blood sample of approximately 5–10 mm^3 was obtained from all patients via the peripheral venous route, before DCCV, 30 minutes following the DCCV procedure, and during the one-month follow up. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) haemogram tubes. BNP levels were immediately assessed using the Bio-Site Triagemeter device and recorded in picograms per millilitre (pg/ml).

In this study, all patients underwent ECG and TTE at the one-month mark. Based on the acquired TTE values, the patients were categorised as having no diastolic dysfunction, impaired relaxation, pseudonormal filling pattern or restrictive features. The patients were then divided into two groups, based primarily on elevated LV filling pressures. The first group included patients without diastolic dysfunction and impaired relaxation, whereas the second group included patients with pseudonormal and restrictive features. BNP levels were reassessed during the first month of the follow up. The study methodology is shown in Fig. 1.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 (IBM Corp, Ar-monk, NY, USA). The Shapiro–Wilk normality test was used to determine which tests were appropriate for the dataset. For data with a normal distribution, parametric tests were performed, and non-parametric tests were performed for the data with no normal distribution. The Mann–Whitney *U*-test was used to compare independent variables between the groups. Wilcoxon analysis was used to compare baseline BNP (during AF), 30-minute BNP and one-month BNP levels. Pearson's correlation analysis was used to determine the correlations between the baseline values. Frequency tables, baseline characteristics and mean values were analysed. Means are expressed as mean ± standard deviation (SD), and *p*-values were considered statistically significant if calculated below 0.05.

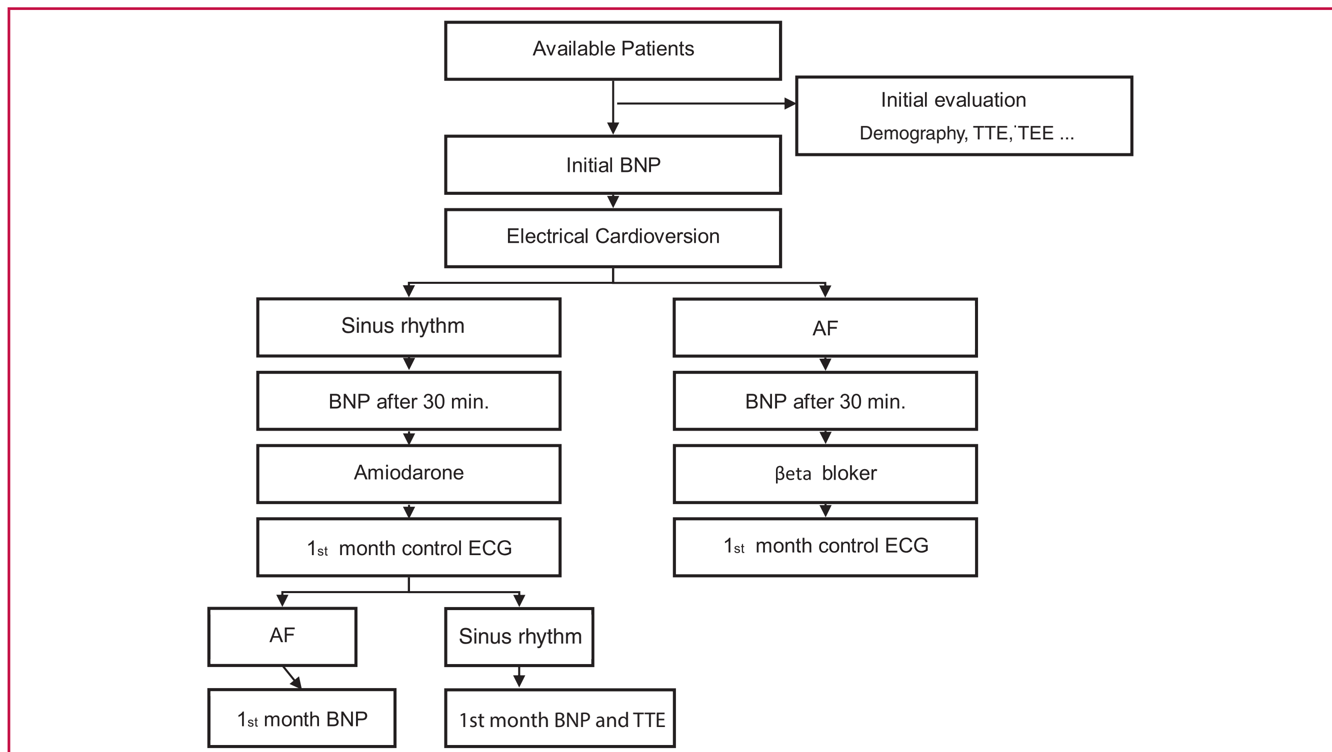

Fig. 1 Methodology of the study.

Results

The study included a cohort of 31 patients, 19 females and 12 males. Table 1 shows the patients' demographic characteristics. The baseline BNP levels ranged from 51 to 874 pg/ml. The mean BNP level was 241 pg/ml. Only six patients (19.35%) had BNP levels below 100 pg/ml. The patients' heart rates varied from 68 to 142 beats/min, with a mean heart rate of 104 beats/min in 31 patients. Approximately 50% of the patients had heart rates between 101 and 120 beats/min. The results of the TTE and TEE performed prior to cardioversion are shown in Table 2.

Correlation analysis revealed a positive relationship between baseline BNP levels before DCCV, baseline heart rate, and the peak E/Em ratio before cardioversion. Conversely, no correlation was found between the patients' age and baseline BNP levels, baseline heart rate, and peak E, peak Em and peak E/Em.

Table 1. The demographic characteristics of the patients

Demographics	*Number (%)*
Gender	
Male	12 (39)
Female	19 (61)
Age (year)	
< 65	6 (19)
65–74	16 (52)
>75	9 (29)
Diabetes mellitus	
Yes	8 (26)
No	23 (74)
Hypertension	
Yes	24 (77)
No	7 (23)

Table 2. TTE and TEE results before cardioversion

Variables	*Number*	*Minimum*	*Maximum*	*Mean*
LVEF (%)	31	51	73	61.13 ± 12.5
LVEDD (cm)	31	4.0	5.4	4.5 ± 0.9
LVESD (cm)	31	2.4	3.9	3.0 ± 0.3
LA (cm)	31	3.8	4.8	4.4 ± 0.6
IVS (cm)	31	1	2	1.2 ± 0.2
LVPWD (cm)	31	0.9	1.3	1.1 ± 0.1
Peak E (cm/s)	31	65	142	100.07 ± 34.21
Peak Em (cm/s)	31	8	32	14.73 ± 9.67
Peak E/Em	31	3.60	18.40	7.54 ± 7.85
LAA flow rate (cm/s)	31	16.5	70.0	38.023 ± 14.56

LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: left atrium, IVS: interventricular septum, LVPWD: left ventricular posterior wall thickness, LAA: left atrial appendage.

Table 3. Correlation analysis

Variable 1	*Variable 2*	R	*p-value*
Basal BNP	Basal heart rate	0.429	0.016
Basal BNP	Peak E/Em	0.378	0.036
Basal BNP	Peak E	0.33	0.07
Basal BNP	Peak Em	−0.202	0.276
Basal BNP	Age	0.248	0.179
Basal heart rate	LVDD	−0.298	0.1
Basal heart rate	Peak E	0.180	0.33
Basal heart rate	Peak Em	−0.126	0.501
Basal heart rate	Peak E/Em	0.345	0.057
Basal heart rate	Age	−0.200	0.281
Peak E	Peak Em	−0.102	0.58
Peak E	Peak E/Em	0.689	< 0.001
Peak Em	Peak E/Em	−0.564	0.001

BNP: brain natriuretic peptide, LVEDD: left ventricular end-diastolic diameter.

Table 4. Comparing baseline variables of patients with early recurrence of AF with patients who remained in SR

	Early recurrence (mean ± SD)		
Variables	*Yes* (n = *4*)	*No* (n = *24*)	p-*value**
Age	67.75 ± 12.5	69.29 ± 14.6	0.322
Basal heart rate	107.5 ± 28.7	103.5 ± 25.6	0.635
LVEF (%)	63.25 ± 10.7	61.12 ± 9.5	0.465
LVEDD	4.27 ± 0.9	4.5 ± 1.1	0.144
LA	4.25 ± 0.8	4.42 ± 1.2	0.186
Peak E/peak E′	6.95 ± 1.9	7.71 ± 2.1	0.825
LAA flow rate	23.58 ± 4.5	38.41 ± 5.1	0.186
BNP basal (pg/ml)	448.5 ± 48.6	224.28 ± 22.3	0.09
BNP 30-min (pg/ml)	318.5 ± 39.7	153.42 ± 11.9	0.05

LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: left atrium, LAA: left atrial appendage.
**p* < 0.05 means statistically significant differences.

Further details of the correlation analysis are presented in Table 3.

DCCV was performed for all 31 patients enrolled in the study. Of these, 28 patients successfully converted to SR, while three patients did not. Comparison of the 28 patients who successfully underwent cardioversion with the three patients who did not, no statistically significant difference was observed in variables such as baseline demographics and echocardiographic findings. Although baseline BNP levels were lower in patients who failed to achieve SR, this difference was not statistically significant.

Notably, a statistically significant decrease in heart rate was observed in patients who achieved SR after DCCV ($p < 0.0001$). Conversely, there was no statistically significant change in heart rate in patients who did not achieve SR ($p = 0.102$).

In a cohort of 28 patients who achieved SR by DCCV, four patients experienced a recurrence of AF within the first month (referred to as early recurrence), while 24 patients maintained SR. When comparing patients who experienced early AF recurrence with those who remained in SR, there were no statistically significant differences in age, heart rate, ejection fraction and baseline BNP levels. However, the baseline BNP values tended to be higher in the early recurrence group. In particular, the mean BNP level at 30 minutes after DCCV was significantly higher in the early recurrence group. These findings are detailed in Table 4.

In this study, patients were divided into three groups based on their rhythm status, and BNP levels were assessed at baseline, 30 minutes after DCCV, and during a one-month follow up (Table 5). A more detailed description of the results for each group is provided below.

Group 1 (successful cardioversion and SR): this group included cases in which cardioversion successfully restored SR. Statistical analysis showed a significant difference in BNP levels at the three time points (baseline, 30 minutes post DCCV and one-month follow up) with $p < 0.0001$.

Table 6. BNP levels during follow up in patients according to diastolic dysfunction

	Diastolic function (mean ± SD)		
BNP values (pg/ml)	*Group 1* (n = *10*)	*Group 2* (n = *14*)	p-*value**
Basal BNP	146.4 ± 13.7	279.92 ± 32.9	0.022
BNP at 30 min	96.6 ± 7.9	194.021 ± 26.7	0.022
BNP at 1 month	47.86 ± 8.7	137.91 ± 16.8	0.002

**p* < 0.05 means statistically significant differences.

Group 2 (early recurrence after cardioversion): patients in this group initially achieved SR after DCCV but experienced early recurrence. Upon achieving SR after cardioversion, a significant decrease in BNP level was observed. However, at the one-month follow up, BNP levels showed a subsequent increase when AF reccurred.

Group 3 (failure to achieve SR with cardioversion) consisted of patients in whom DCCV failed to restore SR. No significant differences were observed in BNP levels between the three time points in these patients.

These results suggest that variable changes in BNP levels depend on the success of cardioversion and the maintenance of SR. Group 1 showed a significant overall change in BNP levels, while group 2 showed a decrease immediately after cardioversion but a subsequent increase at the one-month follow up. Group 3, with unsuccessful cardioversion, did not show a significant change in BNP levels. The observed changes in BNP levels may be associated with successful cardioversion, and BNP fluctuations with patients with arrhythmias.

In the first month of follow up, the 24 patients who maintained SR were divided into two groups based on the one-month echocardiographic findings. The first group included patients without diastolic dysfunction and impaired relaxation, whereas the second group included patients with pseudonormal characteristics and restrictive features.

In particular, the second group had significantly higher initial BNP, 30-minute BNP and one-month BNP levels than the first group. These results are detailed in Table 6.

Demographic data, baseline heart rate and echocardiographic findings were compared between patients with and without diastolic dysfunction. Patients with diastolic dysfunction were significantly older ($p < 0.001$). However, there were no significant differences between the two groups with regard to the other variables studied.

Discussion

Our study reveals that BNP levels measured 30 minutes after DCCV were better predictors for maintaining SR post cardioversion, compared to baseline BNP levels. Additionally, echocardiographic diastolic dysfunction in AF correlated with BNP levels before cardioversion. Patients with SR

Table 5. BNP monitoring in patient groups

Variables	*Basal BNP (mean ± SD) pg/ml*	*BNP at 30 min (mean ± SD) pg/ml*	*BNP at 1 month (mean ± SD) pg/ml*
SR after DCCV and remains in SR	224.28 ± 22.3	153.42 ± 11.9	100.39 ± 9.8
SR after DCCV and early recurrence at 1 month	448.5 ± 48.6	318.5 ± 39.7	484.25 ± 51.6
No SR	107.3 ± 20.1	98.26 ± 12.7	116.33 ± 14.7

SR: sinus rhythm, BNP: brain natriuretic peptide, DCCV: direct-current cardioversion.

after cardioversion exhibited BNP levels before DCCV, 30 minutes after DCCV and at one month of follow up that correlated with the severity of diastolic dysfunction assessed by echocardiography.

In the normal heart, endocrine function is mainly located in the atria. Atrial myocytes actively express and release natriuretic hormones, which play a crucial role in regulating fluid balance and blood pressure. These hormones, particularly atrial natriuretic peptide (ANP) and BNP, are released in response to atrial distension. However, in ventricular disease, the gene expression of ANP and BNP is also activated in ventricular myocytes.[19] BNP, a neurohormone, is initially synthesised as a prohormone in the heart's response to increased myocardial wall stress, caused by increased volume or pressure overload, among other factors. BNP is secreted from the atria in patients in normal SR and in patients with AF.

Tuinenburg *et al*.[20] investigated atrial BNP gene expression in patients with paroxysmal and persistent AF and identified the atrium as the primary site of BNP gene expression. Furthermore, Silvet *et al*.[21] observed a significant increase in BNP levels following atrial stretch and volume overload, demonstrating a close association with chronic AF. In addition, pathological changes such as atrial enlargement and fibrosis may contribute to increased BNP production.[22] Elevated BNP levels can also suggest an increased degree of systemic inflammation, which is associated with AF.

Notably, only inflammatory cytokine-induced BNP gene expression showed a distinct difference in the regulation of cardiac BNP gene expression, unlike ANP.[23] While the elimination half-life of BNP is typically around 20 minutes in a healthy population, it can decrease to approximately 10–12 minutes in patients experiencing conditions such as volume overload, congestion, haemodynamic instability, increased renin–angiotensin system activity and increased neutral endopeptidase activity.[24,25]

Stretching of the atrial wall caused by elevated atrial pressure represents another significant mechanism during AF. The absence of atrial contraction resulting from this tension causes an unfavourable alteration in the LV filling pattern.[26]

Our study found that BNP levels were not effective in determining the success of cardioversion. It was also found that BNP levels tended to be lower in the group of patients in whom cardioversion failed. This finding is related to the limited number of patients in whom cardioversion failed, making it difficult to accurately assess the success of cardioversion based on BNP levels. In addition, basal BNP levels correlated with basal heart rate and peak E/Em ratio. It is possible that in AF, the variability of the AF rate reduces the reliability of BNP in assessing cardiac structure and function.

In our study, early recurrence of AF was observed in four of 28 patients, whereas 24 patients had SR in the first month. The mean difference in basal BNP levels between the two groups did not reach statistical significance ($p = 0.09$). In contrast to our study, two meta-analyses showed a significant association between basal BNP levels before DCCV and the maintenance of SR.[14,27]

A statistically significant difference in the 30-minute BNP levels was observed between the group with early recurrence of AF and the group with maintained SR. Furthermore, 30-minute BNP levels had predictive value for the maintenance of SR at the one-month follow up. The rapid decrease in plasma BNP levels after DCCV may be attributed to the shift from AF to SR, a decrease in heart rate and changes in cardiac status.

In addition, BNP has a short half-life of less than 20 minutes. The BNP value at 30 minutes after DCCV may provide a more reliable assessment of cardiac structure and function, unaffected by heart rate variations. Our results are consistent with those of the study by Ari *et al*., which showed that the BNP levels at the 30-minute mark were associated with the the maintenance of SR over the six-month follow-up period.[28]

LV diastolic dysfunction creates a profibrillatory environment that promotes the onset and recurrence of AF.[15,16] Therefore, our study aimed to assess diastolic function by using TTE in all patients at baseline. In addition, the follow-up patients remained in SR for the first month. Our study showed a significant correlation between baseline BNP levels and the pre-DCCV peak E/Em ratio. This supports the findings of Lee *et al*., who showed significant correlations between BNP levels and the LA volume index, as well as E/Em, in patients with AF.[29]

In addition, after one month of follow-up echocardiography in patients with SR, the low LV filling pressure group, consisting of normal and impaired relaxation patterns, had significantly lower basal, 30-minute and first-month BNP levels than the high LV filling pressure group, consisting of pseudonormal and restrictive patterns. Patients with no or mild diastolic dysfunction had significantly lower BNP levels than those with moderate and severe diastolic dysfunction.

In a population-based study of 840 elderly patients with no history of atrial arrhythmias, there was a strong and independent association between the presence and severity of diastolic dysfunction and a higher risk of developing non-valvular AF (NVAF). The five-year age-adjusted Kaplan–Meier curves of NVAF were one, 12, 14 and 21% for patients with normal, abnormal relaxation, pseudonormal and restrictive LV diastolic filling, respectively.[30]

The primary limitation of this study is the restricted number of participants. Another limitation is that we did not investigate echocardiographic parameters, such as left atrial volume index, which is well known to be associated with diastolic dysfunction, success in achieving SR after cardioversion, and prediction of AF recurrence after successful cardioversion.

Conclusion

When deciding on a strategy for AF, BNP values measured 30 minutes after DCCV were a better predictor of maintained SR post cardioversion than baseline BNP values, which could have been affected by heart rate. Echocardiographic diastolic dysfunction in AF correlated with BNP values before cardioversion. The combined assessment of pre-cardioversion BNP values and echocardiographic diastolic dysfunction parameters, as well as the amount of decrease in BNP values at 30 minutes after cardioversion, may be useful in selecting a control strategy for patients with AF.

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