Evaluation of In-Hospital NT-proBNP Changes in Heart Failure Patients to Identify the Six-Month Clinical Response Following Cardiac Resynchronization Therapy

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Abstract- N-terminal pro β-type natriuretic peptide (NT-proBNP) is a valuable marker for monitoring the response to treatment in patients with heart failure. Based on the clinically observed improvement of heart failure symptoms early after cardiac resynchronization therapy (CRT), we sought to investigate whether CRT induce any significant reduction in the plasma level of NT-proBNP in three days after implantation and whether it is correlated with patients' response at six months. In this prospective study, 21 consecutive patients with severe heart failure (New York Heart Association class 3.19±0.40) who underwent CRT were enrolled. Being alive, no hospitalization due to decompensated heart failure, and improvement of at least one NYHA functional class at six months were classified as clinical responsiveness. The plasma level of NT-proBNP was measured before, three days, and six months after CRT. Clinical evaluation, echocardiographic study, and six-minute walking test were performed before and six months after the procedure. At six months' follow-up, 16 (76.2%) patients were responders. The plasma level of NT-proBNP at three days after CRT increased almost equally in both responder and non-responder groups of patients (ΔNT-proBNP was 40.94±135.74 *vs*. 54.80±88.98); however, at six months' follow-up, the NT-proBNP changes statistically differed across the two groups of patients (P=0.005). According to our findings, NT-proBNP percent deviation from baseline to three days after CRT appears to be not correlated with the patients' clinical response after six months, which was incongruent to the patients' clinical improvement after CRT.

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Introduction

Heart failure (HF) is a complex syndrome that could be a complication of any structural or functional cardiac disorder; not only caused by contractile force reduction, but also neurohormonal changes affecting sympathetic tone and renin-angiotensin-aldosterone system (1,2). There have been many advances in the pharmacological and non-pharmacological managements of HF over the years, yet the prognosis of severe HF remains poor (3-5).

Cardiac resynchronization therapy (CRT) is an effective non-pharmacological treatment for patients with advanced drug refractory HF and electromechanical asynchrony (6). Large multicenter clinical trials such as the CARE-HF (Cardiac Resynchronization in Heart Failure) study and the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial (7-9) demonstrated that CRT could improve the left ventricular (LV) function electrically and mechanically. CRT also improves HF symptoms and exercise capacity

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in appropriately selected patients and also reduces mortality, morbidity, and hospitalization due to decompensated HF (9-12). Nevertheless, despite appropriate case selection, approximately 20-30% of patients do not respond to CRT (13,14).

B-type natriuretic peptide (BNP) and the inactive aminoterminal fragment, N-terminal proBNP (NT-proBNP), are synthesized in the ventricular myocardium and released in response to volume expansion or pressure overload (15, 16). The higher the BNP and NT-proBNP levels, the greater the severity of HF. These markers are also valuable for the monitoring of the response to treatment (13,17,18). BNP messenger RNA had a high turnover and it could be synthesized in bursts (19,20). Consequently, the plasma level can theoretically change rapidly in response to hemodynamic changes. Relying on this concept and considering that despite equimolar secretion the half life of NT-proBNP is longer than that of BNP in the serum (120 minutes *vs*. 20 minutes) and (15,21), we hypothesized that the synchronization and improvement in the LV function as a result of CRT could affect NT-proBNP and cause a rapid reduction in its plasma level. Also, many patients practically express that they feel much better early after CRT. The current study, therefore, sought to investigate whether CRT induce any significant reduction in the plasma NT-proBNP level in very early post-implantation phase (three days after the procedure) and whether it is correlated with patients' response to treatment at six months.

Materials and Methods

Patients' selection

In this prospective pilot study, we enrolled 21 consecutive patients who underwent CRT due to advanced HF in Tehran Heart Center (THC). The inclusion criteria were QRS complex duration ≥ 120 ms with a left bundle branch block pattern, sinus rhythm, LV ejection fraction (LVEF) ≤ 35%, and New York Heart Association (NYHA) functional class II-IV despite optimal medical treatment for at least three months. Patients with unstable clinical status, acute HF, recent myocardial infarction or coronary revascularization procedure (< three months before), and chronic atrial fibrillation were excluded. This study was approved by the Ethics Committee in our center in accordance with the Declaration of Helsinki, and informed consent was obtained from all the enrolled patients.

Study protocol and follow-up

Clinical examination, twelve-lead electrocardiography (ECG), drug history, tissue Doppler transthoracic echocardiography (TDI), six-minute walking test, and blood sampling were performed for all the patients before and six months after the procedure. Additionally, blood sampling for the NT-proBNP measurement was also performed three days after CRT. Patients who were alive, had no hospitalization due to decompensated HF, and experienced improvement of at least one point in NYHA functional class at six months were classified as being clinical responders.

Echocardiography

Transthoracic two-dimensional and continuous-wave Doppler with color-flow imaging echocardiographic studies were conducted with a commercially available ultrasonographic system (VIVID 7, Vingmed GE, Horten, Norway with a 3.5-MHz transducer). Right and left ventricular dimensions (VD), left ventricular end systolic volume (LVESV), and left ventricular end diastolic volume (LVEDV) were measured according to the guidelines of the American Society of Echocardiography. Additionally, the LVEF was evaluated with the Simpson method.

CRT implantation

The patients received biventricular pacemakers with or without the implantable cardioverter-defibrillator (ICD). The implanted devices were Insync III and Insync Marquis by Medtronic, and Frontier and Epic HF by St. Jude's.

After coronary sinus angiography, the LV leads were inserted transvenously via the subclavian route. The preferred position was lateral or posterolateral vein, but other veins were used if there was implant failure. The right atrium (RA) and right ventricle (RV) leads were implanted at the RA appendage or lateral wall and at the basal or septal region of the RV.

Blood sampling and NT-proBNP assay

Blood sampling was performed at 8 A.M. before, three days, and six months after implantation following resting in supine position for thirty minutes. The samples were transferred into a chilled tube containing 10 mg/ml ethylenediaminetetraacetic acid (EDTA) and 500 U/ml Aprotinin. The tubes were placed on ice and centrifuged at 18-25°C. The plasma was restored at -70°C until assay.

Elecsys® proBNP kits (Roche, Switzerland) were utilized for measuring NT-proBNP. The results are

depicted in pg/ml.

Statistical analysis

The data are presented as mean±SD (standard deviation) for the numerical variables, and summarized by absolute frequencies and percentages for the categorical variables. The continuous variables were compared using the Student t-test or non-parametric Mann-Whitney U test whenever the data did not appear to have normal distributions, while the categorical variables were compared using the Chi-square or Fisher's exact test, as appropriate. The association between the continuous variables was assessed using the Pearson correlation coefficient (r).

The differences in the NT-proBNP level (pg/ml) between the two groups of responders and non-responders were determined via a two-way repeated-measures analysis of variance (ANOVA) across the duration of the study (baseline, three days after CRT, and six months after CRT).

For the statistical analysis, the statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) was used. All p values were two-tailed, with statistical significance defined by *P*-value≤0.05.

Results

Amongst the 21 patients enrolled in our prospective study (mean age=58.24±10.64 years, male=61.9 %), 16 (76.2%) were responders. The baseline clinical characteristics and medications are shown in table 1. There was no significant difference between the responders and non-responders with respect to age, gender, NYHA functional class before CRT, and history of coronary artery disease. Also, no significant difference was found in terms of medications between the two groups (Table 1). The comparisons of the clinical and echocardiographic characteristics at baseline versus six months' follow-up and the responders versus non-responders are presented in table 2.

NT-proBNP

At baseline plasma level of NT-proBNP and despite a remarkable difference (approximately 474 pg/ml) between the responders and non-responders (higher in the responders), the difference was not statistically significant, most probably because of the small sample size (Table 2, Figure 1). In contrast to our expectations, the plasma level of NT-proBNP at three days after CRT increased almost equally in both responder and non-responder groups of patients (ΔNT-proBNP was 40.94±135.74 *vs.* 54.80±88.98); however, at six months' follow-up, the NT-proBNP changes between the responders and non-responders were significant (*P*=0.005). The interaction term between response (responders or non-responders) and time (baseline, three days after CRT, and six months after CRT) was also incorporated into the model, which did not reach a statistically significant level (*P*=0.143), although an apparent interaction was seen on the plot derived from the tests of between-subject effects (Figure 1). The reason is due to the small sample size of the study, especially of the non-responders. Furthermore, the main effects of response and time were also not significant (*P*=0.606 and 0.732, respectively).

Table 1. Baseline characteristics of the study group overall, the responders and non-responders.

Variables	All patients (n=21)	Responders (n=16, 76.2%)	Non-responders (n=5, 23.8%)	*P*-value
Baseline characteristics				
Age, yr (mean±SD)	58.24±10.64	56.50±10.16	63.80±11.35	0.187
Male, n (%)	13 (61.9%)	9 (56.3%)	4 (80%)	0.606
Female, n (%)	8 (38.1%)	7 (43.8%)	1 (20%)	
CAD, n (%)	11 (52.4%)	10 (62.5%)	1 (20%)	0.149
QRS duration, ms (mean±SD)	155.60±31.02	161.67±31.57	137.40±23.00	0.133
NYHA class, (mean±SD)	3.05±0.59	3.19±0.40	2.60±0.89	0.262
Medication				
Loop diuretic, n (%)	17 (81.0%)	12 (80%)	4 (80%)	0.999
Spironolactone, n (%)	13 (61.9%)	9 (60%)	3 (60%)	0.999
Beta-blocker, n (%)	17 (81.0%)	12 (80%)	4 (80%)	0.999
ACEIs or ARB, n (%)	18 (85.7%)	12 (80%)	5 (100%)	0.539
Digoxin, n (%)	17 (81.0%)	11 (73.3%)	5 (100%)	0.530
Anti arrhythmics, n (%)	5 (23.8%)	4 (26.7%)	1 (20%)	0.999

ACEIs: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CAD: Coronary artery disease.

Table 2. Comparison of clinical and echocardiographic data at baseline and six months after CRT.

Variables	Responders (n=16)	Non-responders (n=5)	*P*-value
Clinical			
NYHA class			
Baseline	3.19±0.40	2.60±0.89	0.220
6month after CRT	1.62±0.61‡	2.80±0.84	0.003
ΔNYHA(after - before)	-1.56±0.51	0.20±0.45	< 0.001
QRS duration, ms			
Baseline	161.67±31.57	144.25±19.81	0.133
6month after CRT	132.40±15.10‡	136.25±15.31	0.597
ΔQRS,ms (after - before)	-29.27±35.00	-8.00±28.60	0.281
Six-minute walking			
Baseline	167.13±69.13	272.00±138.95	0.169
Six months after CRT	460.94±108.75‡	270.00±162.17	0.007
Δ Six-minute walking test (after - before)	293.81±99.52	-2.00±61.30	<0.001
Echocardiographic			
LVDd,			
Baseline	67.44±11.16	63.80±8.23	0.511
Six months after CRT	65.88±12.72	66.80±10.43	0.885
LVSd, mm			
Baseline	58.25±11.93	57.60±9.84	0.913
Six months after CRT	53.19±13.75‡	57.40±11.72	0.545
LVEF,%			
Baseline	24.38±6.80	24.00±4.18	0.909
Six months after CRT	31.25±10.08‡	26.00±8.94	0.311
ΔLVEF,% (after - before)	7.50±6.83	2.00±5.70	0.127
LVEDV			
Baseline	223.57±105.79	203.80±46.81	0.786
Six months after CRT	204.00±115.58	232.20±85.43	0.548
LVESV			
Baseline	172.93±95.96	159.60±44.80	0.861
Six months after CRT	152.64±106.83†	170.60±75.47	0.648
Diastolic filling ratio,%			
Baseline	37.18±10.55	27.40±12.68	0.124
Six months after CRT	41.00±11.91	42.50±9.15	0.996
LAB			
NT-proBNP			
Baseline	1092.69±838.51	618.00±485.96	0.248
Three days after CRT	1133.63±874.48	672.80±472.08	0.279
Six months after CRT	793.62±690.20	1363.75±646.42	0.164
Δ NT-proBNP-1 (after three days - before)	40.94±135.74*	54.80±88.98*	0.957
Δ NT-proBNP-2 (after six months - before)	-383.62±159.30*	615.75±179.89*	0.005

LVDd: Left ventricular diastolic dimension; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; LVSd: Left ventricular systolic dimension; NT-proBNP: N-terminal pro B-type natriuretic peptide. * Mean±SEM, difference between baseline and six months after CRT: † $P < 0.05$ and ‡ $P < 0.01$.

Clinical parameters

QRS duration had a significant reduction at six months amongst the responders. Also, a comparison between the six-minute walking test results of the two groups of patients before and six months after implantation showed a statistically significant improvement (Table 2).

Table 3. The Pearson correlation coefficients between the percent changes of six-minute walking test, QRS duration, LVSd, LVESV, LVEF, NYHA class at 6 months, and NT-proBNP before and 3 days and 6 months after CRT.

	Δ 6-minutes walking (%)	Δ QRS (%)	Δ LVSd (%)	Δ LVESV (%)	Δ LVEF (%)	Δ NYHA functional class (%)	Δ NT-pro BNP (Before *vs.* after 3days - %)	Δ NT-pro BNP (Before *vs.* after 6months - %)
Δ *Six-minute walking test (%)*	1							
Δ *QRS (%)*	0.134	1						
Δ *LVSd (%)*	-0.033	-0.028	1					
Δ *LVESV (%)*	0.147	0.267	0.238	1				
Δ *LVEF (%)*	-0.468	-0.200	-0.240	-0.161	1			
Δ *NYHA functional class (%)*	-0.521*	0.261	0.034	0.174	-0.089	1		
Δ *NT-proBNP (Before vs. after three days- %)*	-0.194	-0.038	0.052	0.207	0.089	-0.098	1	
Δ *NT-proBNP (Before vs. after six months- %)*	-0.160	0.226	0.482	-0.171	0.122	-0.273	0.432	1

LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; LVSd: Left ventricular systolic dimension. * $P \leq 0.05$, all data are presented as Δ (%) which is the percent changes in each of the variables from baseline to six months of follow-up , Δ NT-proBNP (Before *vs.* after three days - %): percent change in NT-proBNP from baseline to three days after CRT.

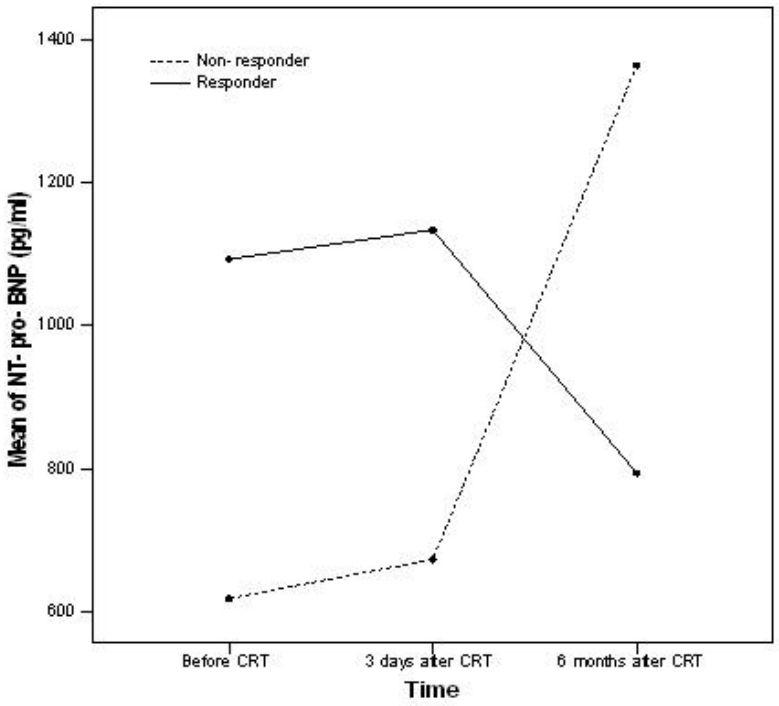

Figure 1. Plasma level of NT-proBNP before, three days, and six months after cardiac resynchronization therapy in responder and non-responder groups of patients.

Echocardiography

A significant decrease in LVSd and LVESV was observed in the responders. In addition, the LVEF increased significantly after six months in the patients who had responded to CRT. The changes in the other echocardiographic parameters, including LVDd, LVEDV, diastolic filling ratio, albeit in the anticipated directions, were not statistically significant during the

follow-up and between the two groups due to the small sample size of the study.

Correlations

The Pearson correlations comparing the percent changes of the six-minute walking test, QRS duration, LVEF, LVSd, LVESV and NYHA functional class before versus 6 months after CRT, and NT-proBNP percent changes before versus three days and six months after CRT are depicted in table 3.

There was no correlation between the percent changes of NT-proBNP after three days and the percent changes of the six-minute walking test, QRS duration, LVEF, LVSd, LVESV and NYHA class as a measure for response (r=0.194, -0.038, 0.052, 0.207, 0.089, and -0.048 respectively). The percent changes of NT-proBNP, QRS duration, LVESV and LVEF after six months were similarly uncorrelated (r=0.226, -0.171 and 0.122, respectively). Although the percent changes of NT-proBNP and LVSd after six months tend to be correlated (r=0.482) but not significant in this sample size (P=0.095).

Discussion

In this pilot study, we found that the early changes in plasma NT-proBNP three days after CRT could not predict the clinical response at six months' follow-up. We observed an approximately equal increase of NT-proBNP in both groups of responders and non-responders three days after CRT (ΔNT-proBNP was 40.94±135.74 *vs.* 54.80±88.98, respectively). Afterwards, during the six-month follow-up period, the trend of the NT-proBNP changes with respect to response to CRT was rational.

To our knowledge, despite a large number of studies have documented an acute hemodynamic improvement, including cardiac output and pulse pressure and decrease in pulmonary artery and wedge pressure after CRT (22-27) there was no study evaluating BNP or NT-pro BNP changes within days after CRT. For instance, Pitzalis *et al.* found that plasma BNP levels > 91.5 pg/ml at one month after CRT was correlated with HF progression after twelve months (3). Another study by Glick *et al.* evaluated the baseline plasma BNP levels in the peripheral venous blood and coronary sinus during biventricular implantation and within two weeks afterwards to predict clinical response and mortality during a mean 17.7±8.2 months of follow-up (8). Their results demonstrated that the BNP change from baseline to two weeks after implantation was the only independent factor that predicted mortality (P=0.029, hazard ratio= 0.993, 95% CI= 0.986-0.999) and a decrease of 18.3 pg/ml in the BNP plasma level two weeks after CRT could significantly discriminate patients' response to CRT with regard to survival. They also suggested that the baseline coronary sinus BNP level was significantly elevated compared to the peripheral venous blood (P=0.01) and that it could predict CHF-related hospitalization during follow-up (8).

In some studies the relation between BNP or NT-pro BNP changes during hospitalization and cardiovascular events investigated in patients received standard medical treatment due to acute decompensated HF. Bettencourt *et al.* enrolled 182 patients admitted to hospital due to decompensated HF who received diuretics, ACE inhibitors, and β-blockers (28). They observed that a decrease of > 30 % of the baseline level during hospitalization was significantly concomitant with better prognosis and less readmission and mortality due to HF within six months of discharge (28). Di Somma *et al.* showed that a decrease of BNP level of more than 46% and a BNP absolute value < 300 pg/ml at hospital discharge were powerful negative prognostic values for cardiovascular events during a six-month follow-up period (29). A pilot study designed by James *et al.* appraised the interrelationship between blood volume, BNP, and hemodynamic changes from admission to 12-24 hours after acute treatment in patients admitted to the Intensive Care Unit (ICU) for pulmonary catheter-guided treatment for HF (20). They concluded that the blood volume change had better correlations with hemodynamic status in comparison with the BNP changes. As a result, it seems that the plasma BNP level reveals the long-term volume status more accurately than instantaneous volume status and there is a lag of BNP levels behind the clinical picture (20). This incongruity was implicit before in two small studies of the patients who had undergone electrical cardioversion to treat atrial fibrillation and the patients with symptomatic bradycardia due to sick sinus syndrome or atrioventricular block with no clinical evidence of congestive HF. They posited that BNP levels increase during cardiac pacing and higher pacing rates lead to a more dominant increase in the plasma BNP levels (30,31).

In line with aforementioned studies, the BNP and NT-proBNP percent deviations from baseline to early after treatment appear to be partially different in the setting of medical treatment versus CRT for advanced HF. In our daily practice, we have witnessed several

patients experiencing considerable improvement in their symptoms in the very early post-implant phase. Although in some patients it may be the placebo effect, it is probable that it is the beginning of a favorable clinical response among clinical responders. This slight early post-implant increase of NT-pro BNP was not significant and was incongruent to the patients' clinical improvement after CRT. Remodeling is a predictor of mortality in congestive HF, and CRT can also reverse the remodeling process and improve clinical outcomes (13,32). Explanation could be first the main mechanism of the favorable effects of CRT on the LV function and BNP as a marker reflecting the LV function is the "cardiac reverse remodeling" due to synchronization, which does not occur in the very early phase of CRT. Second, the aforementioned effects of cardiac pacing on BNP can be seen in CRT cases as well.

Finally, according to our secondary results the pre-implantation NT-proBNP level was remarkably higher amongst the responders than that of the non-responders. Nonetheless, this difference between the two groups was not statistically significant in our pilot study. It is noticeable that A great deal of controversy exists surrounding the relation between the pre-implantation plasma levels of BNP and the clinical response to CRT. The El-Saed *et al*. study demonstrated that patients with higher BNP levels before CRT had significantly more hospitalization and mortality rates due to HF compared to those with lower BNP levels (33). In contrast, Lellouche *et al*. evaluated the value of the baseline plasma BNP level to predict the response to CRT in patients with HF (34). Their results showed that the CRT responders exhibited a higher baseline BNP level and the baseline BNP level could independently predict the CRT response (P=0.001) (34). More studies are necessary to clarify the impact of pre-implantation NT-pro BNP level on the long-term response to CRT.

Study limitations

The major limitation of our pilot study is the small sample size, which can affect our results. We are, however, hopeful that this study will lead to more investigations on the optimum time for evaluating NT-proBNP after CRT to accurately predict advance HF patients' outcome and optimize decision-making. In conclusion, in our pilot study, we observed an approximately equal increase of NT-proBNP in both groups of responders and non-responders three days after CRT. According to our results it can be concluded that the BNP and NT-proBNP percent deviations from baseline to early after treatment are partially different in the setting of medical treatment versus CRT for advanced HF and maybe it is not an accurate measure for evaluating the clinical response to CRT at six months. This slight early post-implant increase was incongruent to the patients' clinical improvement after CRT.

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