The Egyptian Journal of Critical Care Medicine (2016) 4, 97–103

The Egyptian College of Critical Care Physicians

The Egyptian Journal of Critical Care Medicine

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ORIGINAL ARTICLE

Usefulness of plasma B type natriuretic peptide as a predictor to identify responders following CRT

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Received 29 October 2015; revised 20 March 2016; accepted 19 May 2016
Available online 31 May 2016

KEYWORDS

BNP;
CRT;
Heart failure

Abstract It has been shown that patients with heart failure have high levels of brain or type B natriuretic peptide (BNP), and that there is a correlation between these and the severity of their condition. Many studies report that monitoring BNP levels could be a sensitive method for diagnosing heart failure and performing risk stratification, and that they could act as an independent predictor of adverse events helping clinicians arrive at a prognosis.

To achieve this purpose we studied 30 patients with CHF (27 males, mean age 57 years) undergoing CRT implantation.

The main finding of our study was that CRT exerted a substantial reduction in plasma BNP levels among responders, but no significant change in nonresponders after 3 months follow-up, only responders showed a significant decrease in plasma BNP levels (229.64 pg/ml ± 111) as compared to non-responders (468 pg/ml ± 96) P value <0.01. Response could be predicted with a cut-off value of 360 pg/ml, with a sensitivity and specificity of 90.9% and 87.5%, respectively.

In conclusion, BNP monitoring is potentially a good prognostic indicator of LV functional recovery and reverse remodeling after CRT can accurately identify echocardiographic responders after CRT. Percentage change in plasma BNP levels from baseline to 3 months was the strongest predictor of long-term response to CRT and may have potential to predict outcome.

1. Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with moderate-to-severe heart failure (HF) and ventricular dyssynchrony. CRT improves Cardiac function, quality of life (QoL), and life expectancy in patients with HF [1–4]. Biventricular pacing improves symptoms (New York Heart Association [NYHA] class), exercise tolerance (6-min walk distance), and quality-of-life scores by decreasing dyssynchrony in patients with advanced chronic HF [5–7]. Cardiac resynchronization therapy (CRT) optimizes ventricular loading conditions, improves systolic function,

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Peer review under responsibility of The Egyptian College of Critical Care Physicians.

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http://dx.doi.org/10.1016/j.ejccm.2016.05.003

and reduces mitral regurgitation, thereby leading to reverse remodeling [5,6,8].

However, lack of response to CRT has been reported in up to 30% of patients [6,8,9]. On the basis of these considerations, a variety of parameters, including echocardiographic ventricular dyssynchrony [10], QRS reduction after implantation [11], and the location and extent of myocardial scarring [12], have been reported to be predictors of the response to CRT, but disappointing results from PROSPECT study indicated the limitation of these parameters [13].

There has been growing interest in identifying new markers for dyssynchrony and the techniques to optimize device settings to increase the true-responder rate, in addition to optimal medical management [14–17]. CRT-induced reverse remodeling could reduce neurohormonal activity in addition to improving anatomic and functional parameters.

Brain natriuretic peptides (BNP) and its inactive amino terminal portion (NT-pro BNP), are neurohormones released by the ventricle in response to increase LV wall stress. Hence, BNP level may play a valuable role for the assessment of cardiac dysfunction, particularly LV dysfunction, and for monitoring of the response to cardiac therapy [18,19]. Decrease in BNP associated with drug treatment in patients with CHF correlates with improvement in hemodynamic parameters [20–22], clinical status and prognosis, including number of hospitalizations for deterioration of CHF [23,24]. Fruhwald et al. [25] showed that CRT leads to an early and sustained decrease in NT-pro BNP potentially reflecting improvement in LV function. In responders, left lateral wall pacing increases systolic function, reduces mitral regurgitation (MR) and thus decrease the wall motion stress. In this favorable remodeling process, neurohumoral activity is reduced and the decrease in plasma B-type natriuretic peptide after initiation of CRT predicts clinical improvement during follow-up [26].

1.1. Aim of work

The aim of this study was to evaluate the effect of CRT on plasma concentrations of β-type natriuretic peptide (BNP) and the value of BNP in predicting the clinical response to CRT.

2. Patients and methods

Over a period of one year from September 2012 to November 2013, thirty patients who received a biventricular pacing system were studied. They included 27 males and 3 females, with a mean age of 57.5 ± 6 years.

The patients were studied at the (Critical care department) Cairo University.

2.1. Inclusion criteria

- Advanced CHF (NYHA class II-IV) despite optimized drug therapy including angiotensin converting enzyme inhibitors or Angiotensin receptor antagonists, diuretics, beta-receptor blockers and spironolactone when tolerated.
- Intraventricular conduction delay (QRS $\geqslant$ 120 ms) in the form of left bundle branch block.
- Left ventricular ejection fraction (LVEF) $\leqslant$35% as assessed by echocardiography.

2.2. Exclusion criteria

(1) Patients with uncontrolled HF requiring hospital admission or not on stable medical therapy for the last three months; (2) serum creatinine level $\geqslant$2 mg/dl; (3) myocardial infarction within previous 3 months; (4) previous valve replacement or reconstructions.

2.2.1. The studied patients were subjected to baseline assessment including

Informed written consent, Full history taking and clinical examination, twelve lead ECG, NYHA class, blood pressure, heart rate, CHF compensation status and QRS duration were assessed during each clinical follow-up visit, and their exercise capacity was assessed by a 6-min walk test.

2.3. All patients were subjected to

2.3.1. Biochemical assays

BNP level was assessed in the absence of uncontrolled HF one to 10 days before implantation. Blood samples were drawn from an antecubital vein in the morning before and 3 months after the implant. Blood for measurement of plasma BNP was transferred to a chilled tube containing *ethylenediaminetetraacetic acid* (EDTA) (1 mg/ml) and aprotinin (500 kallikrein inactivator U/mL). Test tubes were immediately centrifuged. Plasma samples were stored at −70 °C until assay. Plasma BNP concentrations were measured using a specific immunoradiometric assay (non-extracted) for human BNP. (RayBio®, USA) done at our unit Lab. The analysis was blind to the outcome.

2.3.2. Echocardiographic measurements

All patients were subjected to transthoracic echocardiographic examination using ATL.HDI 5000 colored echocardiographic machine using a 3.5 MHz transducer (PHILIPS).

Two-dimensional Doppler-flow echocardiography was performed at baseline and at follow up to assess left ventricular (LV) ejection fraction (EA), diastolic dimensions and the degree of mitral regurgitation quantification (from grade 1 to 4). LVEF was calculated using the single plane method. The analysis was blinded to the outcome.

2.4. Study protocol

Peripheral blood samples for analysis of BNP were drawn at baseline and 3 months after initiation of CRT. At baseline, history, clinical status, drug therapy, echocardiographic parameters and Exercise capacity testing were evaluated. Three months after implantation of the CRT system, clinical status, drug therapy and echocardiographic data were assessed.

2.5. Criteria to define responders

2.5.1. Clinical criteria

- > 1 point decrease in NYHA functional class [27,28].

2.5.2. Echocardiographic criteria

- A reduction of LVESV by 15% or greater after CRT [13,29,30].

2.6. Statistical analysis

Quantitative variables are expressed as mean value ± SD, whereas qualitative variables are expressed as number and percentage. Descriptive analysis was performed for all relevant continuous variables. Comparison between groups was done using chi-square for qualitative variables & independent samples, *T*-test for normally distributed quantitative variables. Quantitative variables not normally distributed were compared using non-parametrical Mann–Whitney test & Kruskal–Wallis Test. Logistic regression analysis was used to examine the predictors of responders for CRT. To evaluate the predictive value of changes in plasma BNP levels, receiver operating characteristic (ROC) analysis was performed, the area under the curve (AUC) calculated and possible cut off points were selected. Statistical significance was set at $P < 0.05$. All data were analyzed using the SPSS v. 12.0 statistical packages.

3. Results

3.1. Demographic data

Age of patients undergoing the study ranged from 42 to 70 years with a mean of 57.5 ± 6.6 years, (90%) were males and 3 (10%) were females (Table 1).

3.1.1. Clinical presentation

3.1.1.1. Underlying heart disease causing heart failure. Of the study group 17 patients (56.7%) had Ischemic heart disease, while 13 (43.3%) were non-ischemic (Fig. 1).

3.1.1.2. NYHA class before PM implantation. Prior to implantation 23 patients (76%) had NYHA class III while 2 patients (6%) had NYHA class II and 5 patients had ambulatory NYHA class IV (16%).

3.1.1.3. Type of pacemaker implanted. Twenty-eight patients (93.3%) had received a CRT-P System, whereas 2 patients (6.7%) had a CRT-D (see Table 2).

3.1.2. CRT response

Among the 30 patients included in this study, 22 (73.3%) were considered Responders to CRT (see Fig. 2).

3.1.2.1. Baseline echocardiographic parameters. Baseline LV volumes and LVEF, were not significantly different between responders and non-responders (see Fig. 4).

Table 1 Baseline data.

Age (yrs)	57.5 ± 6
Men	27
NYHA class (II/III/IV)	2/23/5
LVEF (%)	28.83 ± 4.46
LVEDD (mm)	299.53 ± 41.64
LVESV (mm)	209.5 ± 36.6
Mitral regegurge (mild/moderate/severe)	11/13/6
PM dependency	2
CRT-p/CRT-D	28/2
Ischemic cardiomyopathy	17
Preimplantation QRS(ms)	149 ± 15.17
BNP level (pg./ml)	449.73 ± 86.03
ACEI/ARBs	28
B blockers	21
Diuretics	26
Spironolactone	20
Digoxin	7
6MWT	311 ± 31 m

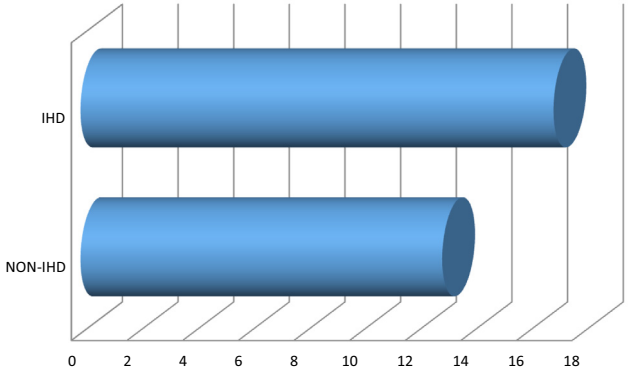


Figure 1 Presence of ischemic heart disease (IHD). As shown in the figure there was no significant difference in the number of patients having IHD in the study population.

3.1.2.2. Underlying cause for heart failure. There was no statistical difference regarding etiology of heart failure between the two groups (p value = 0.407) (see Fig. 3).

3.1.2.3. Baseline QRS width. As seen in the only baseline parameter that was highly significant between Responders and non-Responders prior to CRT implantation was QRS width in surface ECG. The Baseline QRS width ranged between 130–170 ms with a mean of 143 ± 12 in responders, and ranged between 150–180 ms. in non-responders mean 165 ± 10.69) P value was < 0.001.

3.1.3. BNP at baseline and after follow-up

At Baseline the mean BNP level was 464.55 ± 80 pg/ml in Responders and 409 ± 94 pg/ml in Non-Responders with no statistical difference between the two groups (p value 0.120).

However at follow up, only the Responders showed a significant decrease in plasma BNP levels (229.64 pg/ml ± 111) as compared to Non-Responders (468 pg/ml ± 96), P value < 0.001.

Table 2 Baseline parameters.

	Responders	Non-responders	*P* value
Baseline LV parameters			
EDV (mm)	298 ± 42	301 ± 42	0.86
ESV (mm)	209 ± 36	217 ± 40	0.625
EF (%)	29 ± 4	27 ± 4	0.38
Heart failure etiology			0.407
Ischemic	11	6	
Non-ischemic	11	2	
QRS width (ms)	143 ± 12	165 ± 11	<0.001
BNP level (pg/ml)	464 ± 80	409 ± 94	0.120
Total	22	8	

In order to assess the predictive value of the change in BNP in differentiating responders and non-responders, ROC curve and AUC parameters were analyzed.

- Percent change in BNP (ΔBNP%) was associated with the largest AUC (1.000, 95% confidence interval 0.883–1), followed by absolute change in BNP (BNP pg/ml) (AUC = 0.943, 95% confidence interval 0.793–0.992). A drop in ΔBNP% of more than 4.615% differentiated responders from non-responders with 100% sensitivity and 100% specificity.
- A cut-off BNP value of 360 pg/ml had a specificity of 87.5% and a sensitivity of 90.9% in predicting CRT response.

3.1.4. Improvement in echo parameters at follow-up

A statistically significant decrease in left ventricular volumes LVEDV (298.6 ± 42 ml vs. 243.3 ± 37 ml $p < 0.001$) and LVESV (209.5 ± 36 ml vs. 149 ± 28 ml, $p < 0.001$), together with an improvement in LVEF (29 ± 4% vs. 38 ± 4%, $p < 0.001$).

3.1.5. QRS width

As seen in Table 3 the mean QRS width decreased at follow up mainly among the Responders.

3.1.6. Correlation between BNP level and LV volumes and ejection fraction at follow-up

The change in BNP level at follow up had high negative correlation with the change in LVEF ($r = -0.7194$, $P < 0.001$) and a high positive correlation with LV end-diastolic volume ($r = 0.7504$, $P < 0.001$) and LV end-systolic volume ($r = 0.74360.45$, $P < 0.001$).

3.1.7. Correlation between change of BNP level and change of 6 min walk test at follow up

The plasma BNP levels at follow up also showed high negative correlation with the *6 min walk test* at follow up $r = -0.681$ with p value <0.001.

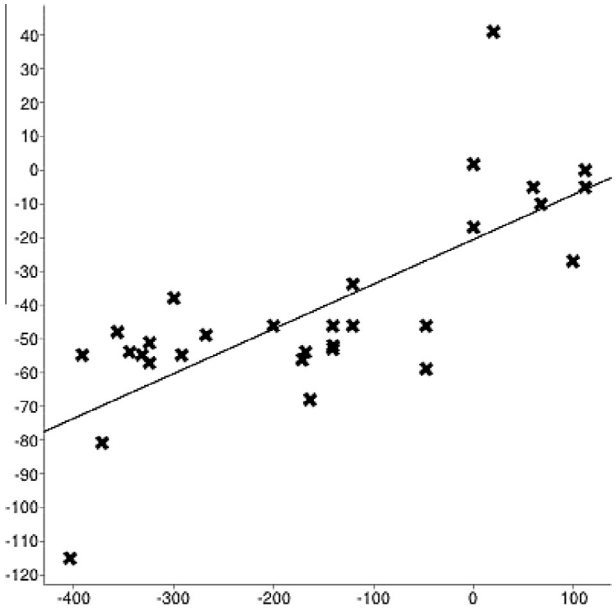
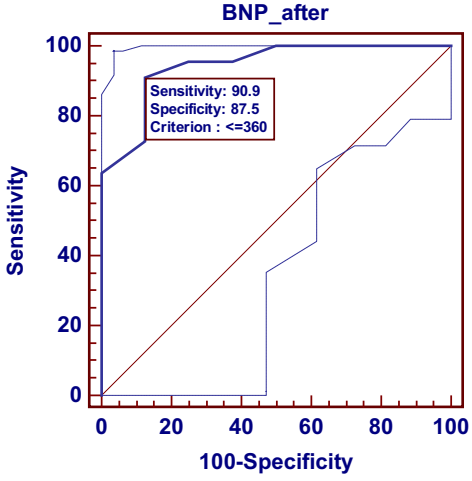


Figure 3 Correlation between changes in LVEDV and plasma levels of BNP at followup ($r = 0.75$, $p < 0.001$).



Area under the ROC curve (AUC)	0.943
Standard Error	0.0594
95% Confidence Interval	0.793 to 0.992
z statistic	7.467
Significance level P (Area=0.5)	0.0001

Figure 2 ROC curve showing BNP level at follow-up.

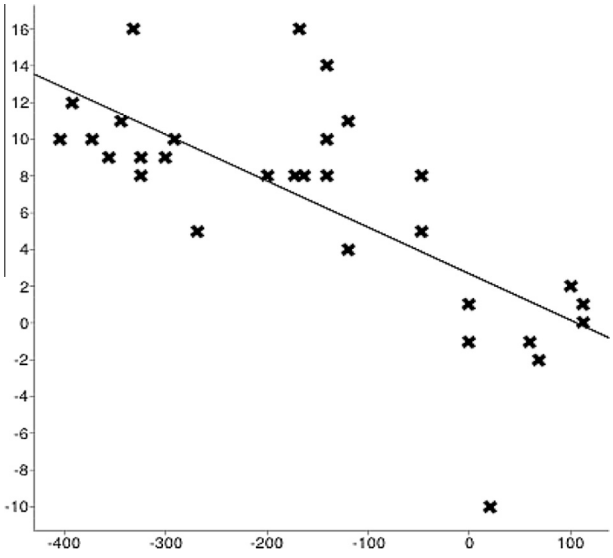


Figure 4 Correlation between changes in LVEF and plasma levels BNP at follow-up ($r = 0.74$, $p < 0.001$).

Table 3 Follow-up parameters among responders and non-responders.

	Responders	Non-responders	*P* value
LV parameters			
EDV (mm)	243 ± 37	299 ± 42	< 0.001
ESV (mm)	149 ± 28	219 ± 39	< 0.001
EF (%)	38 ± 4	27 ± 4	< 0.001
QRS width (ms)	100 ± 14	131 ± 17	< 0.001
BNP level (pg/ml)	229 ± 111	468 ± 96	< 0.001
Total	22	8	

3.1.8. Correlation between QRS width at follow up and 3.1.8.1. LV volumes and ejection fraction. There was high positive correlation between QRS width in surface ECG at follow up with both LV volumes (EDV, ESV) $r = 0.473$ and 0.616 and negative correlation with EF $r = -0.687$ with *p*-value < 0.001.

3.1.8.2. 6 min walk test. The QRS width at follow up had a negative correlation with the *6 min walk test* at follow up $r = -0.68132$ with *p* value < 0.001 (see Table 4).

4. Discussion

Landmark clinical trials such as COMPANION [9] and CARE-HF [10] have shown a survival benefit with CRT. This therapy has opened up a whole new modality in the treatment of HF, focusing on electromechanical assistance to the failing heart.

Although the clinical results of CRT are promising, analysis of individual responses has revealed that almost 30% of patients do not exhibit any symptomatic or hemodynamic improvement: the so-called non-responders [31–33]. One of the reasons for this may be suboptimal programing of the device, which has particular considerations as compared to standard pacemakers [34].

Plasma B-type natriuretic peptide (BNP) is a very useful diagnostic and prognostic marker in stratifying HF patients and guiding optimization of HF treatment. BNP levels correlate well with functional class and hemodynamics and is an independent prognostic indicator in patients with congestive HF, however, the predictive role of preimplantation BNP determination remains unclear [35,36].

5. Main finding

The main finding of our study was that CRT exerted a substantial reduction in plasma BNP levels in responders, but no significant change in non-responders after 3 months follow-up and that change in plasma BNP level between baseline and 3 months after CRT may be useful to identify echocardiographic responders following CRT.

Filzmaier et al. [37] showed significant reductions in BNP levels after only 4–6 days of continuous biventricular pacing. Mortada et al. [38] noted significant reductions ($P < 0.05$) in plasma BNP levels from baseline to 3-month follow-up in 87% of their study participants.

Sinha et al. [39] in 2003 documented significant reductions in BNP levels associated with significant reductions in LV vol-

Table 4 Comparison between the previous studies and the current cohort.

Author	Year	No. of patients	Baseline BNP	Results
Filzmaier et al.	2002	12	537 ± 306 pg/ml	Reduction of BNP levels to 255 ± 200 pg/ml $p < .001$
Sinha et al.	2003	17	700 ± 33 pg/ml	BNP decreased to 503 ± 31 pg/ml after reinitiating CRT therapy $p < 0.01$
Mortada et al.	2005	32	984 ± 38 pg/ml	Reduction in plasma BNP levels in 28 (87%) patients 184 ± 45 pg/ml, $p < 0.5$
Civello et al.	2005	37	Mean 569 pg/ml in responders Mean 624 pg/ml in non-responders	Responders had a delta BNP of −240 ± 66 pg/ml and non-responders had a delta BNP of −16 ± 89 ml ($p < 0.01$)
Kubanek et al.	2006	43	BNP345.3 ± 34 pg/ml big ET1-1 3.11 ± 1.50 fmol/ml	Reduction in neurohormone levels BNP 267.7 ± 320.8 pg/ml, $p < 0.01$, big ET-1 2.50 ± 1.56 fmol/ml $p < 0.05$
Fruhwald et al.	2007	813	Median plasma con. of NT-pro-BNP 1920 pg/mL	The differences in medians at 18 months of follow-up (567 pg/mL $P < 0.0001$)
Our study	2015	30	BNP was 449 ± 94 pg/ml in responders and 464 ± 94 in non-responders	BNP 229 ± 111 in responders and 468 ± 96 in non-responders $p < 0.01$

ume and a significant increase in ejection fraction, which remained consistent throughout long-term follow-up (> 1 year) in patients treated with biventricular pacing.

Fruhwald et al. [25] in 2007 in a study on patients with moderate or severe HF and LV dyssynchrony showed that CRT exerts an early and sustained reduction in BNP level reflecting the improvements in LV geometry and function. Moreover, the Care-HF post-hoc analysis concluded that BNP may be used to monitor CRT effect [40].

Indeed, response to CRT is clearly a multifactorial process including the severity of intraventricular asynchrony, presence and localization of LV viability and lead placement with respect to the latest LV activation site. In contrast, BNP release is essentially determined by LV wall stress. Hence, it is not surprising that baseline BNP is not accurate to predict clinical or echocardiographic response after CRT [41].

5.1. LV remodeling

Furthermore, our results showed that BNP is also a good surrogate marker to identify LV remodeling following CRT as it showed strong correlations with both LV volumes; LVEDV ($r = 0.7504$, $P < 0.001$), LVESV ($r = 0.74360.45$, $P < 0.001$) and LVEF ($r = -0.7194$, $P < 0.001$). More importantly, BNP monitoring allows the clinician to accurately identify echocardiographic responders to CRT. Since LV remodeling predicts outcome with better accuracy than clinical improvement after CRT and that BNP monitoring can identify echocardiographic responders with a very good sensitivity and specificity, assessment of BNP after CRT could be used as an additional tool to assist the clinician in the evaluation of the patient's condition [42].

After adjusting for all variables, neither echo parameters (p value was 0.865, 0.495, and 0.380 for EDV, ESV and EF respectively), nor BNP level (p value 0.120) prior to implantation could predict responders. Only QRS width in surface ECG could predict responders ($p = < 0.01$). A cut-off QRS width of 140 ms had a specificity of 100% and a sensitivity of 59.1% in predicting CRT response.

5.2. Practical implications

Our results may have important implications for management decisions in patients receiving CRT. The long term outcome of CRT could be predicted by changes in BNP level earlier after implant of the CRT system (i.e. after three months). This is supported by the fact that patients at high risk of heart failure progression should be followed more closely and receive more aggressive clinical management, including programing of timing intervals and basic heart rate, fine tuning pacing mode [43] and more aggressive therapeutic strategies.

Furthermore, our study may provide an easy yet reliable surrogate marker to define CRT response. Previous studies use different definitions of CRT response varying from functional parameters (such as NYHA class, 6 min walking test) to reverse LV Remodeling and/or toward morbidity and mortality [44]. The property of BNP to define the CRT response is related to the fact that the peptide reflects the complex functional and anatomical status of the cardiovascular system as a whole and may therefore be a more sensitive parameter of clinical status.

The study is limited however by the relatively small study group, larger studies are needed to further support these findings.

6. Conclusions

- BNP monitoring is potentially a good prognostic indicator of LV functional recovery and reverse remodeling after CRT, and can accurately identify echocardiographic responders after CRT. The findings though are limited to this cohort study.

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