NT-proBNP, MR-proANP and Adiponectin Levels in Monitoring Cardiac Resynchronization Therapy

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ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT), is a therapeutic option for patients with refractory heart failure. We aimed to examine the usefulness of N-terminal pro-brain-type natriuretic peptide (NT-proBNP), mid-regional pro-atrial natriuretic peptide (MR-proANP), and adiponectin in monitoring CRT-induced left ventricular (LV) reverse remodeling, reverse electrical remodeling, and clinical response.

Patients and Methods: We prospectively enrolled 46 heart failure patients who underwent clinical, electrocardiographic, echocardiographic evaluation and blood sampling for measurements of NT-proBNP, MR-proANP, and adiponectin before and 12-months after CRT implantation. LV reverse remodeling (LVRR), reverse electrical remodeling (RER) and clinical response were described respectively as a decrease in LV end-systolic volume (LVESV) ≥ 15% or an absolute increase in LV ejection fraction ≥ 5%, a decrease in intrinsic QRS (iQRS) duration by ≥ 20 ms, and an improvement of NYHA ≥ 1 class.

Results: At 12 months, LV function, and size, severity of mitral regurgitation (MR), clinical status, and QRS duration were significantly improved by CRT. We detected LVRR, RER, and clinical response in 72%, 54%, and 76% of patients, respectively. Both reductions in MR-proANP and adiponectin levels were correlated with decrease in LVESV ($r= 0.51$, $p< 0.05$; $r= 0.50$, $p< 0.05$, respectively). Also, there was an association between reduction in MR-proANP levels and decrease in mitral regurgitation grade ($r= 0.50$, $p< 0.05$). We observed a relationship between decrease in iQRS duration and reduction in MR-proANP levels after CRT ($r= 0.67$, $p< 0.05$).

Conclusion: MR-proANP levels after CRT may reflect electrical response and regression in MR. Furthermore, both adiponectin and MR-proANP levels after CRT may reveal decrease in LVESV.

Key Words: Cardiac resynchronization therapy; heart failure; adiponectin, NT-proBNP; MR-proANP.

Kardiyak Resenkronizasyon Tedavisinin İzlenmesinde NT-proBNP, MR-proANP ve Adiponektin Düzeyleri

ÖZ

Giriş: Kardiyak resenkronizasyon tedavisi (KRT), refrakter kalp yetersizliği olan hastalarda bir tedavi seçeneğidir. Çalışmada, N-terminal pro-beyin tipi natriüretik peptid (NT-proBNP), mid-regional pro-atriyal natriüretik peptid (MR-proANP) ve adiponektin biyobelirteçlerinin KRT ile indüklenen sol ventrikül ve elektriksel ters yeniden şekillenmeyle KRT'ye klinik yanıtın izlenmesindeki yararlılığının incelemesi amaçlanmıştır.

Hastalar ve Yöntem: Kardiyak resenkronizasyon tedavisi implantasyonundan önce ve 12 ay sonra NT-proBNP, MR-proANP ve adiponektin seviyeleriyle klinik, elektrokardiyografik ve ekokardiyografik değerlendirmeleri yapılmak üzere 46 kalp yetmezliği hastası çalışmaya dahil edildi. Sol ventrikül ters yeniden şekillenme, ters elektriksel yeniden şekillenme ve klinik yanıt sırasıyla sol ventrikül sistol sonu hacminde %15 azalma veya sol ventrikül ejeksiyon fraksiyonunda ≥ %5 mutlak artış, intrensek QRS (iQRS) süresi ≥ 20 ms ve NYHA ≥ 1 sınıfında iyileşme olarak tanımlandı.

Bulgular: Kardiyak resenkronizasyon tedavisi ile 12. ayda sol ventrikül fonksiyonu ve boyutu, mitral yetersizliğin (MY) şiddeti, klinik durum ve QRS süresinde iyileşme kaydedilmiştir. Hastaların sırasıyla %72, %54 ve %76'sında sol ventrikül ters yeniden şekillenme, ters elektriksel yeniden şekillenme ve klinik yanıt tespit edilmiştir. Hem MR-proANP hem de adiponektin düzeylerindeki düşüş, sol ventrikül sistol sonu hacmindeki düşüşle korelasyon göstermiştir (sırasıyla; $r= 0.51$, $p< 0.05$; $r= 0.50$, $p< 0.05$). Ayrıca, MR-proANP düzeylerindeki azalma ile mitral yetersizlik derecesindeki azalma arasında bir ilişki vardır ($r= 0.50$, $p< 0.05$). Ayrıca iQRS süresindeki azalma ile KRT sonrası MR-proANP düzeylerindeki azalma arasında bir ilişki gözlemlenmiştir ($r= 0.67$, $p< 0.05$).

Sonuç: Kardiyak resenkronizasyon tedavisi sonrası MR-proANP düzeyleri, elektriksel yanıtı ve MY'deki gerilemeyi yansıtabilir. Ayrıca, KRT'den sonraki adiponektin ve MR-proANP düzeyleri, sol ventrikül sistol sonu hacmindeki düşüşü gösterebilir.

Anahtar Kelimeler: Kardiyak resenkronizasyon tedavisi; kalp yetersizliği, adiponektin, NT-proBNP; MR-proANP.

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is a treatment option developed for selected patients with refractory heart failure (HF). The usefulness of biomarkers has been well established in diagnosis, prognosis and monitoring of HF[1]. In this context, biomarkers may be valuable in monitoring effectiveness and response of CRT by reflecting both myocardial reverse remodeling and decrease in left heart filling pressures during CRT[2,3]. Some previous studies suggested that N-terminal pro-brain-type natriuretic peptide (NT-proBNP) can be useful in both predicting response to CRT and monitoring clinical course after CRT[4,5]. Mid-regional pro-atrial natriuretic peptide (MR-proANP), which is another member of natriuretic peptide family, seems superior to NT-proBNP in reflection of left ventricular (LV) filling pressures[2]. Currently, there is only one study which indicated that low circulating MR-proANP levels at the time of device implantation may help to identify patients who will benefit from CRT[6]. However, role of circulating MR-proANP in monitoring response to CRT is still unknown. Adiponectin, another biomarker, has been shown to be a predictor of mortality in HF[7]. As far as we know, only a single study has shown a decline in levels of circulating adiponectin after 12-months of CRT[8].

To our knowledge, no studies have yet compared circulating NT-proBNP, MR-proANP and adiponectin biomarkers with each other in monitoring of CRT response in three categories: LV reverse remodeling (LVRR), reverse electrical remodeling (RER) and clinical response. We aimed to evaluate the role of NT-proBNP, MR-proANP and adiponectin in monitoring effectiveness of CRT in these three categories.

PATIENTS and METHODS

Study Population

We prospectively enrolled consecutive 46 HF patients who have indication for CRT according to recommendations of the European Society of Cardiology between January 2016 and November 2017[9]. Current study was approved by the Local Ethical Committee and Institutional Review Board (decision number and date: 2015/147 and 23.11.2015). All participants signed a written informed consent prior inclusion the study. The study was accomplished in accordance with principles of the Declaration of Helsinki. The study included patients were > 18 years of age with a left ventricular ejection fraction (LVEF) ≤ 35% in sinus rhythm with a QRS duration of at least 130 ms and left bundle-branch block QRS morphology and they were in New York Heart Association (NYHA) functional class ≥ II despite treatment with optimal medical therapy for ≥ 3 months. Exclusion criteria were: (1) acute coronary syndrome and coronary revascularization (< 3 months), (2) malignancy, (3) chronic liver disease, (4) connective tissue disease, (5) chronic renal insufficiency (estimated creatinine clearance < 30 mL/min according to Modification of Diet in Renal Disease equation), (6) pacemaker dependence, and (7) right bundle-branch block QRS morphology or intraventricular conduction disturbance.

All study patients underwent clinical and echocardiographic evaluation before and 12-months after CRT implantation. Blood samples for the measurement of serum MR-proANP, NT-proBNP and adiponectin levels, and intrinsic 12-lead electrocardiogram (ECG) were obtained from all patients before and 12-months after CRT.

Blood Sample Collection and Laboratory Assessments

Peripheral venous blood samples were drawn from each study patient after 30 minutes of rest with patients in supine position. Blood samples were taken into chilled plain tubes containing ethylenediamine tetra-acetic acid and tubes were immediately centrifuged at 3000 rpm for 15 minutes. Serum aliquots were then transferred to microcentrifuge tubes and stored at -80°C until the time of MR-proANP, NT-proBNP, and adiponectin measurements.

Serum MR-proANP levels were measured by commercially available human MR-proANP enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource Inc, San Diego, CA, USA). Serum adiponectin levels were measured by using human adiponectin ELISA kits (eBioscience Inc, San Diego, CA, USA). Serum NT-proBNP levels were measured by electrochemiluminescence sandwich immunoassay (ECLIA, Roche Diagnostics) using Roche Cobas 6000 Modular Analyzer Series system (Roche Diagnostics, Indianapolis, IN).

Echocardiographic Evaluation

Each patient underwent standard transthoracic echocardiographic examination using a commercially available system (Vivid 7, General Electric-Vingmed Ultrasound, Horten, Norway) at rest before and 12 months after CRT implantation. An experienced echocardiographer, who was blinded to patient clinical data, performed all echocardiographic assessments.

Standard apical four-chamber as well as parasternal long- and short-axis views of left ventricular (LV) were used to measure echocardiographic parameters. LV end-diastolic and end-systolic volumes and LV ejection fraction (LVEF) were calculated by biplane Simpson's method. The LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were measured using two-dimensional guided-mode and Doppler echocardiography based on recommendations for chamber quantification[10]. Additionally, quantitative evaluation of severity of mitral regurgitation (MR) was performed by color and continuous wave Doppler echocardiography based on current recommendations[11].

LVRR was defined as a decrease in left ventricular end-systolic volume (LVESV) ≥ 15%, or an absolute increase in LVEF ≥ 5% afterward CRT implantation[12,13].

Electrocardiographic Evaluation

Standard intrinsic 12-lead surface ECG was recorded with a paper speed of 25 mm/second before and after CRT implantation. 12-month follow-up intrinsic ECG (without biventricular pacing) was recorded after temporarily reprogramming CRT device to VVI 35/minute to allow native rhythm. The intrinsic QRS (iQRS) duration was measured after ensuring a stable QRS morphology for each study patient before CRT and at 12-months follow-up intrinsic ECG. The iQRS duration was measured with a digital caliper on lead presenting widest QRS complex by two independent cardiologists, who were blinded to patient data. The delta iQRS duration (ΔiQRS) was calculated as difference between iQRS duration value at the time of implantation and 12-months after CRT with a positive value indicating a reduction in QRS interval with time.

RER was defined as a reduction in intrinsic QRS (iQRS) duration by ≥ 20 ms 12-months after CRT(14).

Patient with an improvement of 1 ≥ NYHA class at 12-months after CRT was defined as a clinical responder[14,15].

Statistical Analysis

All statistical analyses were performed with SPSS Statistics version 24 (IBM, Armonk, NY). Continuous data were presented as mean ± standard deviation (SD) and categorical data were expressed in percentage (%) or frequency. Normal distribution of continuous data was assessed by Shapiro-Wilk test. The paired Student's t-test was used for comparison of normally distributed continuous variables before and after CRT. Otherwise, we used Wilcoxon signed rank test for skewed continuous variables. The chi-squared test was used to compare categorical data. The relationships between normally distributed continuous variables were determined by Pearson's correlation analysis and Spearman's correlation analysis was used to assess relationships between non-normally distributed continuous variables. The association between categorical variables were examined using Pearson's chi-squared test. A p value < 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of 46 enrolled HF patients are presented in Table 1. CRT implantation was accomplished successfully in all patients without complications. All study patients had follow-up clinical, echocardiographic, electrocardiographic and laboratory assessments at 12 months after CRT (Table 2). Medication regimens of the study patients were indicated in Table 1. No study patient died during the study period.

Table 1. Baseline characteristics of study patients (n= 46)

Characteristics	Value
Age, years (mean ± SD)	63 ± 11
Male gender, n (%)	27 (59%)
Non-ischemic etiology	24 (52%)
Smoking	16 (35%)
History of hypertension	21 (46%)
History of diabetes mellitus	14 (30%)
Systolic blood pressure, mmHg (mean ± SD)	114.3 ± 12.3
Diastolic blood pressure, mmHg (mean ± SD)	68.4 ± 6.2
Creatinine, mg/dL (mean ± SD)	1.06 ± 0.19
Medication	
ACE inhibitor or ARB, n (%)	42 (91%)
Beta blocker, n (%)	43 (94%)
Diuretics, n (%)	33 (72%)
Spironolactone, n (%)	28 (61%)
Digoxin, n (%)	5 (11%)
Ivabradine, n (%)	23 (50%)

ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker.

At 12 months follow-up, NYHA functional class was significantly improved, mean LVEF was significantly increased, whereas LVEDD, LVESD and LVESV were significantly decreased in comparison with baseline. There was a small, and nonsignificant, decrease in LVEDV. Furthermore, degree of MR was reduced significantly at 12 months after CRT (Table 2).

Both paced and intrinsic QRS durations were significantly lower in comparison with baseline at 12 months after CRT. QRS duration decreased significantly by CRT pacing from 158 ± 8 ms to 126 ± 10 ms, p= 0.001, while intrinsic QRS duration decreased from 158 ± 8ms to 138 ± 9 ms, p= 0.001 (Table 2). After 12 months of CRT, significant reductions in serum levels of NT-proBNP, MR-proANP, and adiponectin were observed compared to baseline (Table 2).

At 1-year follow-up with the patients, we detected 33 patients (72%) meeting the prespecified definition of LVRR. RER was identified in 25 patients (54%) according to ≥ 20 ms reduction in iQRS duration and 35 patients (76%) were considered clinical responders based on prespecified definition. 28 patients (61%) showed both LVRR and clinical response, 22 patients (48%) showed both RER and clinical response, and 21 patients (46%) showed both LVRR and RER. Lastly, LVRR, RER, and clinical response were observed together in 20 patients (43%).

Table 2. Comparison of variables at baseline and 12 months after CRT

Variables	Before CRT	12-Mo Follow-up	p value
BMI, kg/m^2	23.92 ± 1.31	24.01 ± 1.28	0.74
NYHA functional class	3.04 ± 0.63	2.15 ± 0.36	***0.001***
LVEF (%)	28.3 ± 3.9	34.4 ± 4.7	0.001
LVEDD (mm)	66.67 ± 7.85	62.54 ± 7.53	0.01
LVESD (mm)	57.50 ± 9.08	53.59 ± 8.53	0.04
LVEDV (mL)	237 ± 73	220 ± 72	0.268
LVESV (mL)	169 ± 66	137 ± 59	0.013
MR grade	2.8	1.8	0.001
QRS duration			
Intrinsic QRS duration (ms)	158 ± 8	138 ± 9	0.001
CRT-paced QRS duration (ms)	158 ± 8	126 ± 10	0.001
NT-proBNP (pg/mL)	2666.87 ± 1672.44	1182.76 ± 535.31	0.001
MR-proANP (pg/mL)	162.08 ± 44.74	109.06 ± 31.75	0.001
Adiponectin (μg/mL)	35.23 ± 15.11	15.80 ± 8.02	0.001

CRT: Cardiac resynchronization therapy, BMI: Body mass index, NYHA: New York Heart Association, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, MR: Mitral regurgitation, NT-proBNP: N-terminal pro-brain-type natriuretic peptide, MR-proANP: Mid-regional pro-atrial natriuretic peptide.

We examined relationships between LVRR, RER, and clinical response using Chi-Square test. We demonstrated a relationship between LVRR and clinical response (X^2= 4.93, p< 0.03; Figure 1). RER was also associated with LVRR (X^2= 4.06, p< 0.05; Figure 1). Ultimately, we found a relationship among RER and clinical response (X^2= 4.27, p< 0.05; Figure 1).

The change in LVESV (ΔLVESV) was correlated with change in LVESD (ΔLVESD) (r= 0.36, p< 0.05) and there was a good correlation between ΔLVESV and change in LVEDV (ΔLVEDV) (r= 0.54, p< 0.01). Moreover, a good correlation was observed between increase in LVEF and decrease in LVESV (r= 0.55, p< 0.01) (Table 3).

There was a good correlation between reduction of MR-proANP and ΔLVESV (r= 0.51, p< 0.05). Moreover, there was a good correlation between reduction of MR-proANP levels and decrease of mitral regurgitation (r= 0.50, p< 0.05). Otherwise, reduction of MR-proANP was strongly correlated with reduction of NT-proBNP 12-months after CRT (r= 0.71, p< 0.01). The reduction of adiponectin was also well correlated with reduction of MR-proANP (r= 0.68, p< 0.01). Additionally, change in serum levels of adiponectin showed a very strong positive correlation with change in serum levels of NT-proBNP (r= 0.79, p< 0.01). We also found a positive correlation between reduction of adiponectin and ΔLVESV (r= 0.50, p< 0.05). Although, the reduction in NT-proBNP levels were significantly correlated with the reduction in adiponection and MR-proANP levels, the change in NT-proBNP serum levels did not show a significant correlation with variables other than biomarkers.

Nevertheless, there was no relationship between improvement in NYHA class and laboratory, electrocardiographic or echocardiographic variables. However, we found a significant positive correlation between reduction of iQRS (ΔiQRS) and change in serum levels of MR-proANP at the end of 1-year follow-up in patients with RER (r= 0.67, p< 0.05).

DISCUSSION

Cardiac resynchronization therapy is a well-known therapy option for advanced HF with a growing number of implantations worldwide. Current study explored roles of NT-proBNP, MR-proANP, and adiponectin levels in monitoring response for CRT. We observed significant improvement in LV function, and size, severity of MR, clinical status, and QRS duration 12 months after CRT. In addition, following 12 months of CRT, we detected significant decreases in serum biomarker levels in comparison with baseline and the decrease in each biomarker was significantly correlated with each other. Our findings also revealed a significant relation between reductions in serum MR-proANP and adiponectin levels and LVESV after CRT.

Cardiac resynchronization therapy ameliorates cardiac function, clinical status and functional capacity while reducing QRS duration, LV dimensions and MR, as confirmed by our current data[16]. Based on our results, CRT significantly reduced NYHA functional class, LV end-diastolic and end-systolic diameters, and LV end-systolic volume and QRS duration, while significantly increased LVEF. The extent of these improvements in LVEF, LV end-diastolic and end-systolic

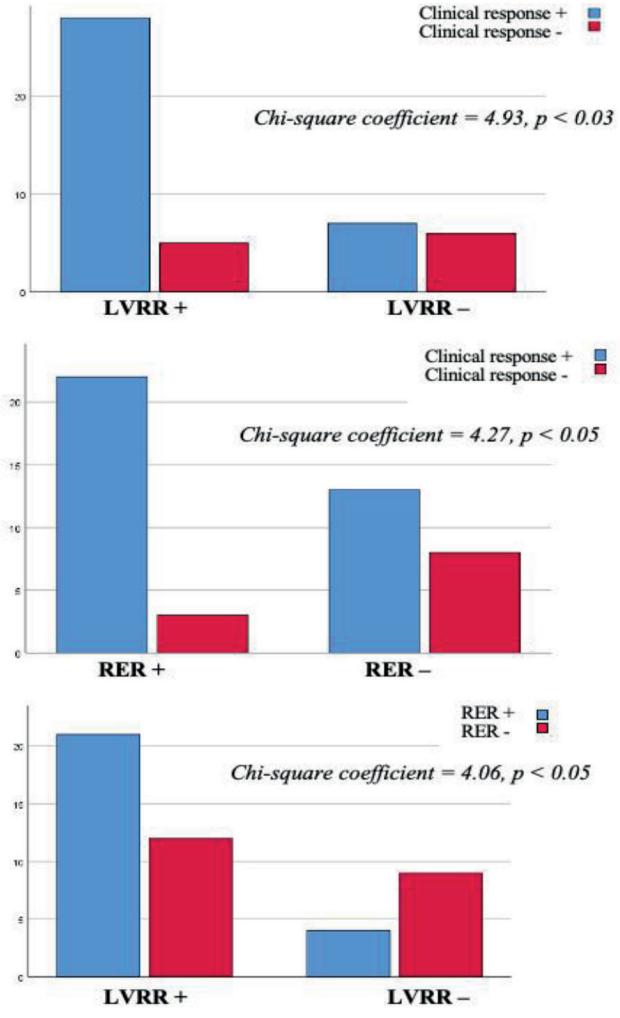

Figure 1. Correlations between LVRR, RER, and clinical response using Chi-square test.

diameters, LV end-systolic volume, QRS duration, clinical status and functional capacity was almost similar to that in previous reports[17,18]. A previous study by van Bommel et al. showed a significant increase in LVEF from 22 ± 8% to 28 ± 9% (p< 0.001) and a significant decrease in LVESV from 167 ± 88 mL to 147 ± 93 mL (p= 0.009), along with a statistically nonsignificant decrease in LVEDV from 211 ± 100 mL to 199 ± 113 mL after CRT(20). In accordance with these findings, we observed a significant increase in LVEF from 28.3 ± 3.9% to 34.4 ± 4.7% (p= 0.001) and an significant decrease in LVESV from 169 ± 66 mL to 137 ± 59 mL (p= 0.013) with a small but nonsignificant decrease in LVEDV from 237 ± 73 mL to 220 ± 72 mL (p= 0.268) 12 months following CRT implantation. A small observational study by Lau et al. also reported a statistically significant decrease in both LVEDV and LVESV 3 months after CRT. On the other hand, our current observation supports their finding of a significant reduction in severity of MR[19]. CRT-induced improvement in severity of MR was also reported by Lancellotti et al. and Madaric et al.[20,21]. The possible mechanisms for reduction in MR after CRT are LVRR and reduction significant relationship between reduction in MR-proANP levels and regression of MR. However, we did not demonstrate a statistically significant relationship between regression of MR and changes in other study biomarkers.

In our study, clinical response, LVRR, and RER occurred in 76%, 72%, and 54% of patients, respectively, at 12 months. Our rate of clinical response is in line with previous reports, but our rates of LVRR and RER are slightly higher than previous reports[14,22]. These divergences with previous findings might be partially explained by somewhat differences in study populations and definition criteria, especially in LVRR criteria. We observed a greater rate of clinical response compared with LVRR and RER responses, as previously indicated in literature[14,22]. Relatively high clinical response rates to CRT may partly be attributable to placebo effect. Perhaps actual symptomatic response rates are less than those calculated in studies, including also our analysis. A meta-analysis by Sohaib et al. in 2013 demonstrated a significant higher rate of clinical

Table 3. Correlations between serum biomarker levels and echocardiographic variables

Variables	ΔLVEDV R	ΔLVESV R	ΔLVEF R	ΔNT-proBNP R	ΔMR-proANP r
ΔLVESD	0.23	0.36*	-0.15	0.28	0.30
ΔLVEDV	1	0.54**	***-0.37***	-0.15	0.02
ΔLVESV	0.54**	1	-0.55**	0.13	0.51*
Δ Mitral regurgitation	0.20	0.28	0.03	0.01	0.50*
ΔNT-proBNP	-0.15	0.13	0.03	1	0.71**
ΔMR-proANP	0.02	0.51*	-0.06	0.71**	1
ΔAdiponectin	0.03	0.50*	-0.15	0.79**	0.68**

* p< 0.05, ** p< 0.01, r= Pearson correlation coefficients.
Δ indicates a change in a variable; LVESD: Left ventricular end-systolic diameter, LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal pro-brain-type natriuretic peptide, MR-proANP: Mid-regional pro-atrial natriuretic peptide.

improvement ascribable to CRT in open studies (20%) where patients in control group had no device versus blinded studies (13%) where all patients underwent CRT device implantation. They concluded that clinical response rates due to solely CRT pacing was fewer than two-thirds, which is currently recognized by scientific community, and they indicated potential placebo effect of CRT in symptom endpoints[23]. Thus, once we examine effect of variables, especially physiological ones, on success of CRT, it can be misleading to consider only clinical response as a success. This was supported by our finding that there is no any significant relation between NYHA class improvement and other variables, although clinical response significantly correlated with both LVRR and RER.

In present study, we observed significant reductions in serum NT-proBNP, MR-proANP, and adiponectin levels 1 year after CRT implantation. In line with our observation, previous studies reported a significant decrease in NT-proBNP levels following CRT implantation[4,5,14]. However, only one study reported a significant reduction in adiponectin levels, in addition to an unchanged in NT-proBNP levels after CRT[8]. Braun et al. also reported a significant reduction in plasma concentrations of NT-proBNP, which was consistent with our result, and a nonsignificant reduction in concentration of NT-proANP after 12 months of biventricular pacing[24]. Moreover, our analysis revealed that decrease in all three biomarkers were well correlated with each other at the end of the 12 months follow-up. In contrast to our analysis, Fruhwald et al. demonstrated both reduction in NT-proBNP and also a relationship between change in NT-proBNP and changes in LVEF and LVESV index as a result of CRT[25]. Additionally, Magne et al. and Yu et al. showed a significant correlation between change in NT-proBNP and changes in LVESV and LVEF after CRT. Therefore, they suggested that reduction of NT-proBNP may reflect LVRR following CRT[5,26]. However, we found no relationship between changes in circulating levels of NT-proBNP and changes in LVEF and LV volumes.

Arrigo et al. showed a reduction in MR-proANP levels 6 months after CRT, especially in CRT responders and they suggested that MR-proBNP may reflect LVRR[6]. Another study by Andersen et al. indicated a significant association between LV filling pressures and MR-proANP at rest and with exercise[2]. Our result, which indicated a positive correlation between reduction in MR-proANP levels and LVESV, supports MR-proANP as a reflector for both LV filling pressures and LVRR. We also observed a good correlation between reduction in MR-proANP levels and decrease in severity of MR. The studies that examined relationship of MR-proANP with LVRR and its role in the prediction and monitoring the response to CRT are limited. Further studies are thus needed to clarify its relation and role in this regard. Again, we found a correlation between reduction of adiponectin levels and decrease in LVESV, but there was no significant relation between reduction of adiponectin levels and regression of MR following CRT. High adiponectin levels have been shown to be associated with severity of HF and poor prognosis[7,27]. Similar to our findings, a significant decrease in elevated adiponectin levels following treatment, as a sign of response to treatment, which may be due to improvement in hemodynamics in HF patients, and a significantly positive correlation between adiponectin and NT-proBNP levels have been reported[27,28]. Moreover, they suggest that a higher decrease in adiponectin levels may indicate a better outcome in acute HF[28]. However, we did not establish a significant relationship between adiponectin levels and clinical response to CRT.

We observed a significant decrease in iQRS duration after 12 months of CRT and a significant strong correlation between decrease in iQRS duration and change in MR-proANP levels. Indeed, to our knowledge, this the first study which suggests that MR-proANP may reflect a decrease in iQRS duration and an improvement in RER. This finding may indicate that MR-proANP can potentially play a role in prediction and monitoring RER following CRT, but this needs further investigation.

LIMITATIONS

There are several limitations to the current study that need to be considered. First, sample size was small, and study was conducted in a single center. Second, blood sampling in our study occurred at two time points. These two biomarker measurements prevented us to evaluate effects of fluctuations in circulating biomarkers with severity of disease. The last limitation was potential placebo effect, which could not be completely eliminated, despite meticulous assessment of clinical response to CRT.

CONCLUSION

Our findings have revealed a direct link between reduction in serum MR-proANP levels and reduction in iQRS duration after CRT. Finally, MR-proANP levels after CRT may reflect electrical response and regression in MR. Furthermore, both adiponectin and MR-proANP levels after CRT can reflect decrease in LVESV. Additional larger and well-designed studies are required to confirm and expand on our findings.

Ethics Committee Approval: The present was approved by the Local Ethics Committee on 23.11.2015 with the decision number 2015/147. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

Informed Consent: All participants signed a written informed consent prior inclusion the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - VP; Analysis/Interpretation - VP, GA; Data Collection - VP, GA; Writing - VP; Critical Revision - VP, GA; Statistical Analysis - VP, GA; Overall Responsibility - VP, GA; Final Approval - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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