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Research Article

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Positive Response to Cardiac Resynchronization Therapy - The Role of NT-proBNP

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Abstract

Background: Cardiac resynchronization therapy (CRT) is effective, but only 60-70% of patients benefit from the therapy. Despite numerous implantations, identification of predictive factors for response is still a challenge. We sought to assess the correlation of echocardiographic and clinical response to baseline demographics in relation to change in NT-proBNP levels at 6 months.

Methods: 211 patients on optimal medical therapy were included retrospectively (72 ± 10 yrs., 66% LBBB, 48% DCMP, 80% male) and investigated at baseline and 6 months later. Improvement of ≥ 1 NYHA class was used as a marker for clinical response, and >15% reduction of left ventricular end-systolic volume was used to define reverse remodeling. NT-proBNP levels were measured at baseline and at 6 months and were compared to echocardiographic and clinical response status.

Results: Four groups were identified: 1) non-responder, 2) echo responder, 3) clinical responder, and 4) double responder (echo and clinical). Responders were younger (70 vs. 74 years, p=0.04), had better NYHA class (2.1 vs. 2.5, p=0.01) and had lower NT-proBNP compared to non-responders at baseline. NT-proBNP slightly increased or remained unchanged in non-responders, whereas reduction in NT-proBNP was of similar magnitude for clinical or echo responders, and was most pronounced for double responders. A reduction of NT-proBNP ≥25% separated non-responders from responders (p=0.01). No significant differences in NT-proBNP levels and no significant changes in NT-proBNP were found across the responder subgroups.

Conclusion: Six-month reduction in NT-proBNP is most pronounced for "double responders, " but was comparable in patients with either clinical or echo response. Lack of NT-proBNP reduction can help identify the non-responders for further intervention.

Keywords

Cardiac resynchronization therapy; Electrocardiography; Echocardiography

Abbreviations

ACEi: Angiotensin Converting Enzyme Inhibitor; AF: Atrial Fibrillation; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CRT: Cardiac Resynchronization Therapy; CRT-D: Cardiac Resynchronization Therapy with Defibrillator Function; CRT-P: Cardiac Resynchronization Therapy without Defibrillator Function; DCMP: Dilated Cardiomyopathy; ECG: Electrocardiogram; EF: Ejection Fraction; EQ5D: Standardized Instrument for use as a Measure of Health Outcome; g: gram; GFR– Glomerular Filtration Ratio; ICMP: Ischaemic Cardiomyopathy; IVCD: Interventricular Conduction Delay; LA: Left Atrium; LBBB: Left Bundle Branch Block; LV: Left Ventricle; LVEDD: Left Ventricular End Diastolic Diameter; LVEDV: Left Ventricular End Diastolic Volume; LVESV: Left Ventricular End Systolic Volume; LVESVi: Left Ventricular End Systolic Volume Index; MI: Myocardial Injury/infarction; ms: millisecond; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NPV: Negative Predictive Value; NYHA: New York Heart Association; NT-proBNP: N-terminal of the Prohormone Brain Natriuretic Peptide; PM: Pacemaker; PPV: Positive Predictive Value; QoL: Quality of Life; RAAS: Renin Aldosterone Angiotensin System; RBBB: Right Bundle Branch Block; SPWMD: Septal-to-Posterior Wall Motion Delay; TAPSE: Tricuspid Annular Plane Systolic Excursion

Background

Cardiac resynchronization therapy (CRT) became available in the late 1990s, offering a safe and effective treatment for patients suffering from heart failure with left ventricular systolic dysfunction (LVEF<35%) and electrical dyssynchrony (QRS duration ≥ 120 ms) [1-3]. However, positive clinical response is observed in only 60-70% of the treated population, and significant echocardiographic remodeling is observed in 50-60% of the treated population [4-6]. The reasons for "non-response" seem to be multifactorial, while different studies have used different definitions of echocardiographic and clinical factors to indicate positive response [4-9]. Using different criteria for response in different studies makes it difficult to make head-to-head comparison of outcome and results as different sub-populations of "responders" may be examined, and there may thus be different implications for clinical outcomes [10]. Additional data from biochemical markers such as NT-proBNP carries a prognostic value in CRT patients, and postoperative reduction has been shown to correlate to reduced long-term mortality [11-13]. Monitoring NT-proBNP may therefore help more easily identify primarily the non-responders for early intervention and more intensive care with a view to improving their quality of life and clinical outcome. Our study sought to compare baseline NT-proBNP levels in relation to clinical and echocardiographic positive response to CRT, and also to assess the association between the extent of change in NT-proBNP levels with echocardiographic and/or clinical response.

Methods

Consecutive patients eligible for CRT therapy were retrospectively recruited from a single tertiary referral center in Sweden from 2011-2014. The study was observational and included patients with indication for CRT according to the ESC guideline recommendations [14]. All patients signed written informed consent prior to enrollment. Clinical data on quality of life was obtained before implantation and at 6 months after implantation when possible. Mortality data was collected from the Swedish registry during this 6-month period. The

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recruitment process is presented in Flowchart 1. A Standard 12 lead-ECG, laboratory examinations and echocardiography were performed within 1 month prior to implantation, and at 6 months after the implantation. Trained physicians followed all patients clinically, and medication was changed as necessary. Standardized formularies and NYHA class estimation were collected at baseline and after 6 months in order to establish subjective clinical response from patients. The local ethics committee approved the study.

Data collection and definition of clinical parameters

Electronic medical records were used in order to retrieve the necessary data, and telephonic interviews were conducted in cases of questionable data or lack of subjective information. Ischemic cardiomyopathy was defined as a history of myocardial infarction and/or cardiac revascularization (CABG or PCI) or ≥ 70% stenosis of two or more epicardial vessels. The absence of an ischaemic event or previous myocardial inflammation such as toxic influence was considered to be dilated cardiomyopathy. Renal disease was considered to be existing in patients where renal failure was diagnosed and in patients where estimated glomerular filtration rate (eGFR) was below 30 ml/min. Lung disease was considered to be existing in patients with medical records of chronic obstructive pulmonary disease diagnosis. Patients on anti-diabetic medication or insulin and patients with diagnosed diabetes in medical records were considered to be diabetics.

NT-proBNP

In most patients, NT-proBNP was collected as part of standard care prior to implantation (n=174) and at 6 months post-implantation (n=165). NT-proBNP samples were analyzed using a Rutenium-based electrochemiluminiscence immunoassay using the accredited method by Roche [15] (Elecsys proBNP assay REF 03121640). The detection interval with this method is between 50-35000 ng/l.

Heart failure symptoms

Minnesota Living with Heart Failure (MLHFQ), EQ5D formularies and Self-Rated Health (EQ VAS) questionnaires were completed and collected at baseline and 6-months post- implantation. Baseline NYHA classification was performed by the operating physician at time of implantation. In 11 cases, clinical symptoms were mild and not clearly distinguished between NYHA class I or NYHA class II in medical records. For those 11 cases, NYHA class I was selected in order to prevent overestimating symptoms for the purpose of this study. At the 6-month visit, the NYHA status was evaluated, and the enrolled study subjects were asked about subjective improvement.

Device implantation

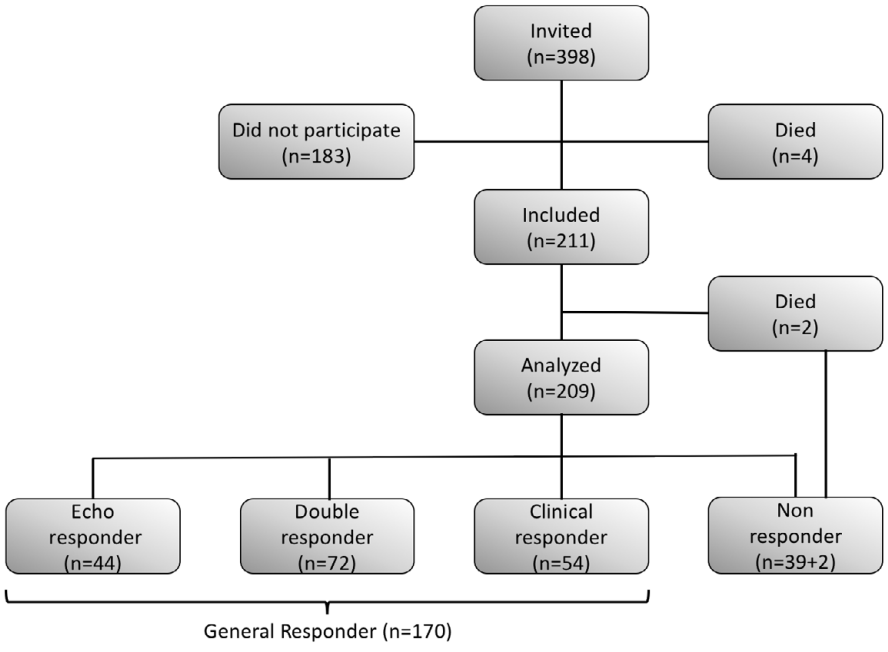
Device implantation was performed in a standard way with left subclavian vascular access. The left ventricular lead was preferably placed in a lateral or posterolateral branch of the coronary sinus. The right ventricular (RV) lead was placed in the RV apex, and the atrial lead was placed in the right atrial appendage. Most patients received a St. Jude Device with the proprietary Quickopt® algorithm turned on, and recommended Quickopt® settings were used. The other patients implanted with the Medtronic device had the device programmed with fixed AV delays of 120/150 ms and simultaneous VV-times.

Electrocardiography

All patients had QRS duration >120 ms. Left bundle branch block (LBBB) was defined as a QS or rS pattern in V1-V2 with broad notched R waves and absence of Q-waves in leads I, V5 and V6 [16]. Right bundle branch block (RBBB) is defined as rSR' morphology in leads V1 or V2, and wave of greater duration than R wave or greater than 40 ms in leads I and V6 in adults [17]. QRS duration exceeding 120 ms without representative morphology for LBBB or RBBB was considered to be intraventricular conduction delay. Pacemaker (PM) rhythm was identified in cases with pacemaker spikes and QRS pattern similar to LBBB [18].

Echocardiography

Standard echocardiographic assessment of the heart was



Flowchart 1: The chart shows the inclusion process and the number of patients in each step.

performed preoperatively and 6 months post-implantation (Vivid E9, GE Medical, Horten, Norway or Philips ie33, Philips Healthcare USA). The collected data was analysed by two trained physicians on a PC workstation using Echopac BT12 software (Echopac BT12, GE Medical, Hortens, Norway). Standard echocardiographic measurements of left ventricular volumes were performed using the recommended Simpson's biplane method [19]. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured, and left ventricular end systolic volume index was calculated (LVESVi) [4-8]. Mitral regurgitation (MR) severity was graded 0-3 according to current guidelines [20]. Septal-to-posterior wall motion delay (SPWMD) was measured as the shortest interval between the maximal displacement of the septum and the posterior wall in milliseconds using M mode measurement from short axis view at the papillary muscle level [21].

Statistical analyses

SPSS statistical software was used for all data analysis (IBM, SPSS ver. 21. 2012, IBM Corporation, New York, USA.). Continuous variables are expressed as means (± standard deviation, SD), and categorical variables are presented as frequencies and percentages. For non-normally distributed continuous variables, the median value with interquartile range (IQR) is presented. Pearson's r test was performed in order to determine the correlation between 2 variables. Differences between groups were assessed using paired or unpaired Student t-tests for continuous variables, the Mann-Whitney U test for variables with non-Gaussian distribution, the χ^2 test for categorical variables, or the Fisher's exact test for unordered categorical variables, as appropriate. With non-normally distributed variables, logarithmic conversion was performed when necessary. ROC analysis was performed in order to identify the suitable cut-off value for positive response. Binary logistic regression was performed in order to investigate predictors for different types of CRT response. A multivariate logistic regression model was fitted with clinically relevant covariates and variables with a univariate p-value of ≤ 0.15 in logistic regression analysis. A two-sided p-value of < 0.05 was considered to be statistically significant.

Definition of response

Echocardiographic response was defined as a reduction of left ventricular end systolic volume (LVESV) in biplane view (Simpson's method) of greater than 15% [22]. Clinical response was based on the NYHA classification and was considered positive if the NYHA improvement was one class or more. Double response was defined where positive clinical and echocardiographic response presented in parallel. Patients with any type of positive response (clinical, echocardiographic or both) were gathered as general responders. Non-responders were the cases where neither clinical nor echo response was positive.

Results

Overall results

A total of 398 patients were invited by letter to participate in the study after receiving a CRT implant. 211 patients chose to participate. Of those 211 patients, two patients died between time of recruitment and the 6-month follow-up. The demographics of the study population were similar to other published CRT cohorts; baseline clinical characteristics are presented in Table 1. At the time of CRT implantation, the patients were on optimal medical therapy with the highest tolerable dosage of standard heart failure medications 87% (n=184) were on Beta blockers, 95% (n=200) were on ACEi or ARB, and 53% (n=112) were on aldosterone blockade). The measured echocardiographic parameters showed significant improvement; the left ventricular ejection fraction increased from 27 ± 8% to 35 ± 13% (p<0.01). At the same time, both systolic (148 ± 62 ml to 119 ± 62.2ml, p<0.01) and diastolic volumes (203 ± 73 ml to 173 ± 72.5 ml, p<0.01) of the left ventricle showed a significant reduction, and similar trends were observed in the left ventricular mass (356 ± 116 g to 301 ± 100 g, p<0.01) and left atrial volume (97.6 ± 42 ml to 86.2 ± 32 ml, p<0.01).

Paired data for NT-ProBNP was available in 34 out of 38 non-responders, 42 out of 54 NYHA responders, 38 out of 44 echo responders and 59 out of 72 double responders. Overall, there was a reduction in NT-proBNP levels from a median value of 1911 ng/l (IQR: 3483) to a median of 1053 ng/l (IQR: 2277), p<0.001. Hemoglobin levels increased from 135 ± 15 g/l to 137 ± 14 g/l, p=0.015, and a slight deterioration in creatinine (108 ± 59 mmol/l vs. 112 ± 53 mmol/l, p=0.03) was observed. Clinical improvement was observed in NYHA class (from 2.4 ± 0.8 to 1.7 ± 0.63, p<0.001), in the Self Rated Health (EQ VAS, from 59 ± 18% to 73 ± 16%, p=0.014) and in the MLHFQ score (from 43 ± 20 to 24 ± 16 p<0.001).

Assessment of the appropriate cut-off level of NT-proBNP change as a selective factor

In order to identify the proper cut-off level of NT-proBNP, ROC analysis was performed in each responder subgroup (i.e. clinical response, echo response, double response). The goal was to identify a cut-off value with suitable sensitivity and specificity for positive response in each responder subgroup. Based on results from

Table 1: Study of Population characteristics.

	Overall (N=211)	Non-Responders (N=41)	Responders (echo- or clinical) (N=170)	P value
Male	80%	82%	79%	0.78
Age (years)	71.6 ± 9	74 ± 7	71 ± 9	0.04
BMI	28	28.2 ± 3	28.16 ± 5	0.47
Hypertension	59%	63%	57%	0.49
Hyperlipidaemia	42%	61%	43%	0.04
Renal disease	13%	25%	9%	0.01
Pulmonary disease	12%	16%	12%	0.45
Diabetes	23%	27%	21%	0.38
CABG	29%	48%	25%	<0.01
Myocardial Infarction	52%	64%	49%	0.09
Non-ischemic aetiology (DCMP)	48%	34%	51%	0.03
PCI	31%	23%	33%	0.20
LBBB/RBBB/PM/ IVCD	66/2/16/16	54/7/25/14	67/1/13/19	0.05
QRS duration	164 ± 24	161	164	0.50
No AF/Parox/Perm	50/24/26%	43/20/36	51/26/23	0.06
Previous PM/ICD	16/9%	20/11%	14/8%	0.39/0.34
CRT-D	76%	73%	77%	0.55
Baseline NT-proBNP	1911 ng/l [IQR 3483]	3016 ng/l [IQR 4172]	1823 ng/l [IQR 3635]	0.19

AF: Atrial fibrillation; BMI: Body mass index; CABG: Coronary artery bypass surgery; CRT-D: Cardiac resynchronization therapy with defibrillator function; DCMP: Dilated cardiomyopathy; IVCD: Interventricular conduction delay; LBBB: Left bundle branch block; MI: Myocardial injury/infarction; PM: Pacemaker; RBBB: right bundle branch block

the different analyses, a cut-off value of -25% carrying the highest sensitivity for separation between responders and non-responders (with an acceptable specificity) was chosen as the cut-off. In the clinical responder group, ROC analysis with 25% NT-proBNP reduction showed 68% sensitivity and 50% specificity, with AUC=0.63. In the Echo responders, sensitivity was 69% with specificity at 56%, and the AUC was 0.62. Similar results were observed in the double responder group, with sensitivity of 73%, specificity of 57%, and AUC of 0.63. For general responders, sensitivity was 68%, specificity was 61%, and AUC was 0.66.

Comparing *non*-responders with general responders, general responders (both echo and clinical) were younger (71 ± 9 vs. 74 ± 7 years, p=0.039) and had lower incidence of renal disease (9% vs. 25% p=0.01) and ischemic cardiomyopathy (49% vs. 66%, p=0.03). The echocardiographic parameters at baseline were similar for both non-responders and general responders, although responders had smaller LV size, smaller left ventricular end-systolic volume index (LVESVi) and more dyssynchronous motion as assessed by septal-to-posterior wall motion delay (SPWMD) (217 ± 111ms vs. 172 ± 61ms p=0.009). A positive correlation was observed between positive response to CRT and NT-proBNP reduction (r=0.23, p=0.026).

Changes in the different parameters general responders *vs.* non-responders are presented in Table 2.

At baseline, the median NT-proBNP level in the examined cohort was 1911 ng/l (IQR 3483). Non-responders had a median value of 3016 ng/l (IQR 4172), echo-responders had a median value of 2176 ng/l (IQR 3357), and clinical responders had a median value of 1403 ng/l (IQR 4455). Double responders had a NT-proBNP level of 1867 ng/l (IQR 3310). Significant reduction of the median NT-proBNP at follow-up was observed in the different responder groups (*echo* responders p=0.03, clinical responders p=0.01, and double responders p=0.02); however, change was not significant in the non-responder group (p=0.87). At 6 months, the median relative reduction in % of baseline NT-proBNP was highest in the double-responders (-51%, IQR 53); it was -39%, IQR 65 in clinical responders, and (-31%, IQR 41 in echo responders). There was a slight increase of 12% (IQR 87) in non-responders (p<0.01 in all subgroups) (Figure 1). Reduction of NT-proBNP in % correlated with LVESV improvement (r=0.24, p=0.008) and with NYHA class improvement (r=0.21, p=0.01). At 6-month follow-up, failure to achieve at least at 25% reduction of NT-proBNP was associated with non-response (PPV: 88%, NPV: 53%).

Comparison of clinical responders versus echocardiographic and double responders

The general responders were divided into three subgroups depending on improvement characteristics: echo responders, clinical responders and double responders. 170 of the 211 patients (81%) showed positive clinical effect, significant reverse remodeling on echocardiography, or both, as response to the treatment. 41 of the 211 patients had no improvement at 6 months and were thus classified as non-responders. Among general responders, 32% (n=54 of 170) showed clinical improvement, 26% (n=44 of 170) showed reduction in LVESV parameter on echocardiography, and 42% (n=72 of 170) had improvement in both the echocardiographic parameters and clinical improvement. Differences in baseline parameters were compared in order to help identify greater likelihood of echo- or clinical response. The population characteristics within the three responder subgroups were similar at baseline. Predictors for clinical and echocardiographic response were examined separately in univariate regression analysis; the results are presented in Table 3.

Univariate predictors for clinical response included: Age, LBBB morphology, absence of renal disease (GFR<35 ml/min) and absence of atrial fibrillation. Univariate predictors for echo response included: dilated cardiomyopathy (as opposed to ischemic cardiomyopathy), absence of renal disease (GFR below 35 ml/min) and LBBB morphology on ECG. Presence of LBBB morphology with QRS duration over 150 ms at baseline and LVESV>65 ml/m^2 were independent predictors for both clinical and echocardiographic response. In multivariate logistic regression analysis, age and renal function had no independent predictive value for either type of response. NT-proBNP reduction of at least 25% had an independent predictive value for echocardiographic, clinical and general response in univariate and multivariate analysis (Supplementary Table).

Discussion

In a real-world population of consecutive CRT treated patients, we show that a 25% reduction of NT-proBNP was associated with positive response to CRT, whereas non-responders had no statistically significant improvement in NT-proBNP levels. The reduction levels were similar for echocardiographic responders and clinical responders, which implies that clinical benefit from the treatment can be derived even if there is no objective improvement in echocardiographic parameters. This suggests that different factors may influence different types of responses (i.e. subjective or objective), and it may therefore be appropriate to use additional information from easily accessible markers such as NT-proBNP during early

Table 2: The table shows the change in various baseline parameters at 6 months compared to the baseline value (mean ± SD). Columns 3 and 5 show the comparison of the p-value for baseline vs. 6 month results. The last column shows the p-value change difference between responder and non-responder groups.

	Responders (Echo or clinical or both)		Non-Responders (Neither echo nor clinical)		Difference between groups
	Mean	P value	Mean	P value	P value
Creatinine (mmol/l)	-5.7 ± 31.4	0.02	0.22 ± 19.1	0.94	0.16
NT-proBNP (ng/l)	-1335 ± 3571	<0.01	248 ± 8436	0.88	0.04
Haemoglobin (g/l)	1.8 ±10.9	0.04	1.6 ± 8.4	0.22	0.387
EQ5D	-0.08 ± 3.9	0.83	-0.11 ± 6	0.94	0.83
Self-Rated Health (EQ VAS)	-13 ± 22	<0.01	-11 ± 10	0.05	0.74
MLHFQ	-17 ± 21	<0.01	-8 ± 19	0.25	0.98
NYHA class	-0.89 ± 0.76	<0.01	-0.07 ± 0.33	0.18	<0.01
LVEDd (mm)	3.8 ± 7	<0.01	4.5 ± 13	0.11	0.71
LVESVI (ml/m^2)	-19.2 ± 19.2	<0.01	-0.15 ± 16.7	0.96	<0.01
LVEDV Biplane (ml)	-38 ± 50	<0.01	12 ± 51	0.23	<0.01
LVESV Biplane (ml)	-39 ± 40	<0.01	2 ± 40	0.83	<0.01
EF Biplane (%)	8.9 ± 14.7	<0.01	3.3 ± 8.9	0.07	<0.01
La volume (ml)	-12 ± 36	<0.01	-5.2 ± 47	0.52	0.95
SPWMD (ms)	-112 ± 114	<0.01	-60 ± 66	<0.01	0.01
LV Mass (g)	-62 ± 81	<0.01	-36 ± 59	<0.01	0.05
QAo-QP (ms)	-17 ± 40	<0.01	-23 ± 44	0.01	0.37
TAPSE (mm)	2.1 ± 7.6	<0.01	-0.8 ± 6.3	0.49	0.06

EF: Ejection fraction; EQ5D: *Standardized instrument for use as a measure of health outcome;* La: Left atrium; LV: Left ventricle; LVeDd: Left ventricular end diastolic diameter; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; LVESVi: Left centricular end systolic volume index, MLHFQ: Minnesota Living with Heart Failure Questionnaire; ms: millisecond; NYHA: New York Heart Association; QAo: Time from QRS start to aortic valve opening; QP: Time from QRS start to pulmonary valve opening; SPWMD: Septal-to-posterior wall motion delay; TAPSE: Tricuspid annular plane systolic excursion.

Table 3: Univariate logistic regression analysis for prediction of *echocardiographic* and *clinical response*.

	Echocardiographic Response			Clinical Response		
	P value	**Hazard Ratio**	**(95% C.I)**	**P value**	**Hazard Ratio**	**(95% C.I)**
Age	0.73	1.00	0.98-1.03	0.07	0.96	0.94-1.00
BMI	0.02	0.92	0.87-0.98	0.21	0.95	0.87-1.03
Sex	0.19	1.71	0.76-3.87	0.82	1.08	0.55-2.1
Hypertension	0.02	0.48	0.25-0.88	0.55	0.81	0.41-1.61
Hyperlipidaemia	0.01	0.42	0.22-0.76	0.05	0.5	0.25-0.988
Myocardial Infarction (Previous)	0.07	1.71	0.95-3.19	0.07	0.54	0.27-1.07
Aetiology	0.07	1.66	0.94-3.92	0.36	1.29	0.74-2.24
CRT type (CRT-D vs CRT-P)	0.10	1.82	0.88-3.77	0.07	0.41	0.21-0.78
LBBB>150 msec	0.03	1.86	1.06-3.17	0.01	2.69	1.35-5.28
Atrial Fibrillation	0.13	1.85	0.83-3.88	0.03	0.53	0.27-0.93
Renal disease (GFR < 30 ml/min)	0.03	0.38	0.15-0.91	0.11	0.51	0.23-1.15
SPWMD	0.25	1.00	0.99-1.0	0.04	1.01	1-1.01
LVESVI > 65 ml/m^2	0.04	0.34	0.12-0.93	0.04	1.82	1.03-3.26
Self-Rated Health (EQ VAS)	0.02	1.03	1.00-1.06	0.93	1.0	0.97-1.03
Change of NT-proBNP (%)	0.04	0.42	0.19-0.94	0.02	0.51	0.29-0.91

BMI: Body mass index; GFR: Glomerular filtration ratio; LBBB: Left bundle branch block; LVEDV: Left ventricular end diastolic volume; LVESVi: Left ventricular end systolic volume index; SPWMD: Septal-to-posterior wall motion delay; CRT: Cardiac resynchronization therapy; CRT-D: Cardiac resynchronization therapy with defibrillator function; CRT-P: Cardiac resynchronization therapy without defibrillator function

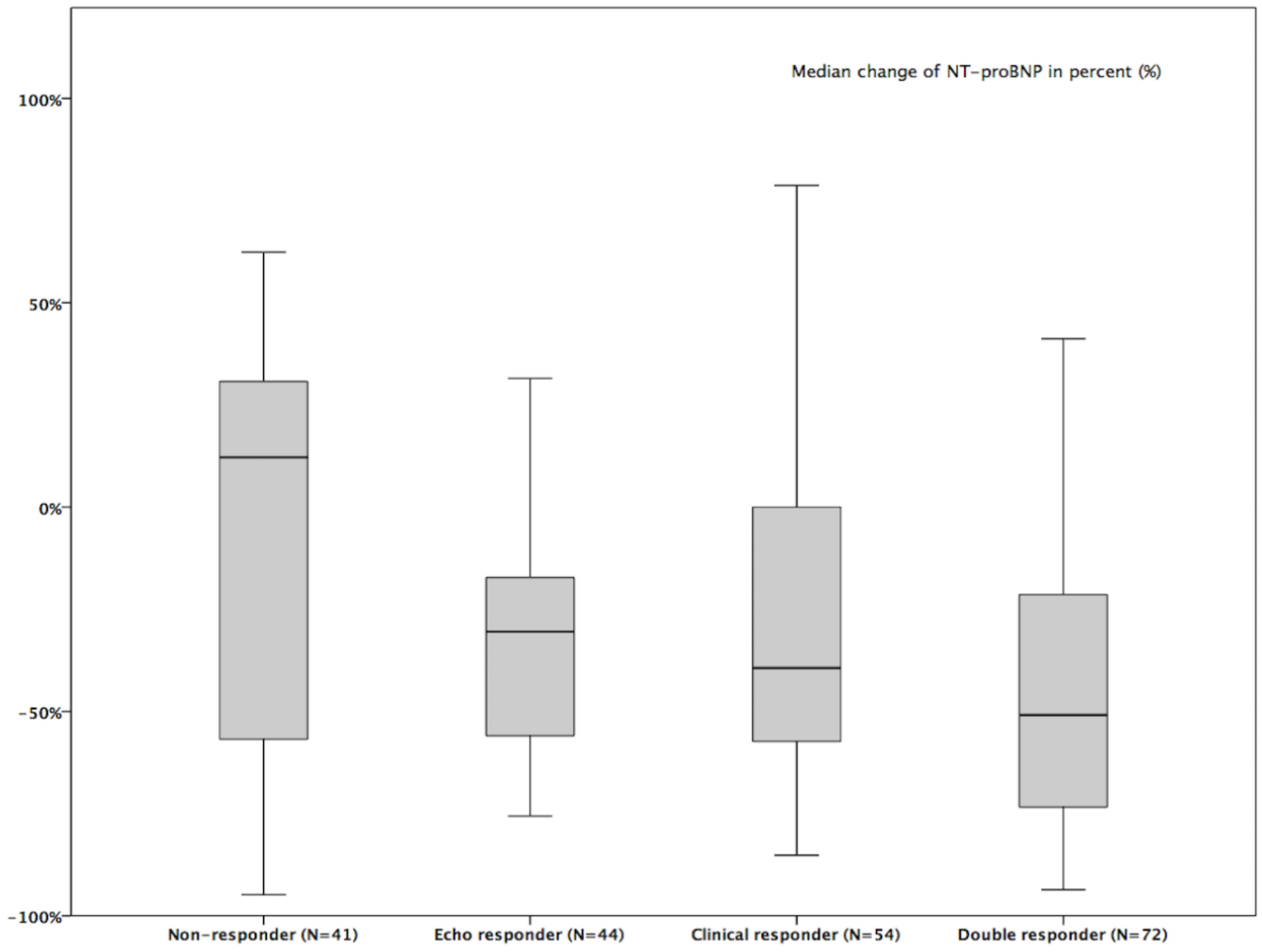


Figure 1: The figure demonstrates the median change of NT-proBNP (in %) from baseline to 6 months in the different subgroups. The positive direction (upward) shows NT-proBNP increase. The negative direction (downward) shows NT-proBNP decrease.

follow-up, with an appropriate cut-off point [23,24]. Using NT-proBNP as a standard tool may help identify "true non-responders" who may benefit most from a tailored therapy with a careful follow-up plan, device optimization and other interventions [25].

Echocardiographic predictors for CRT response

In various studies, several echocardiographic factors have been used to describe improvement, since the ejection fraction plays an important role in selection for CRT. Specifically, mechanical dyssynchrony parameters have been tried as selection variables and have been used to measure outcomes. In the PROSPECT trial, several dyssynchrony measures were evaluated; however, while three measures were correlated to outcome, none was found to be clinically useful, largely due to high intra- and interobserver variability [26]. Kang et al. [27] (in a small trial with 93 patients) created a complex 4-point score system based on tricuspid annular plane systolic excursion (TAPSE), longitudinal strain (LS), and ECG morphology and QRS duration. In this small retrospective patient group, the sensitivity and specificity of this score system was over 80% [27]. Yu et al. [28] published data on 141 patients undergoing CRT and followed up for nearly 2 years. That study found that remodelling of the left ventricle (defined by a reduction of LVESV >10%) had a strong predictive value for long-term mortality. In a recently published study of more than 650 patients, the criterion for echocardiographic response in LVESV was a reduction of more than 15% instead of the previously-used 10% [29]. Interestingly, the result in that study was similar, and a ≥15% LVESV reduction predicted a better clinical outcome. However, clinical improvement together with end systolic volume reduction was observed in only 30% of the cases in that study. Other groups reported similar data, suggesting that LVESV and LVESVi reduction [30] is an important predictor, independent of clinical response [9,31]. Reverse remodelling of the left ventricle seems to be an important predictor for short-term (1 year) and long-term (5 year) outcome, as shown by Foley et al. [32]. Data from the Trust CRT trial was analyzed by Boidol et al. [10], who found that NYHA class improvement (>1 class) and >15% reduction in left ventricular end systolic volume index (LVESVi) were the best predictors of major cardiac adverse event (hospitalization/death). However, in that study, sensitivity was better for the clinical parameters, while specificity was higher for the echocardiographic markers.

The positive response

The definition of "positive response" to CRT varies among different studies [33]. As discussed above, it is not clear which kind of "response" has the best correlation to long-term survival. Therefore, the definition of true positive response to CRT therapy remains controversial, and there is no universal agreement on what interventions are required for identified non-responders. Several studies have suggested that good patient management after CRT implantation can turn the non-responders into responders [34]. However, echocardiographic dyssynchrony parameters alone failed to predict clinical response. Furthermore, time elapsed from the moment of the first heart failure symptom to the moment of implantation did not influence response to the treatment. Factors such as age, sex, QRS duration, LBBB morphology, aetiology and renal function have been described as positive predictors for CRT response, but in our study none of these factors, either alone or in combination, were found to accurately predict which patients would be non-responders. Interestingly, an observational study showed that self-assessed clinical improvement in patients with heart failure is an independent predictor of long-term prognosis, regardless of the baseline ejection fraction [35].

As noted above, the existing data is far from conclusive, and any expansion of the diagnostic portfolio used to identify CRT response (or non-response) is valuable, especially in order to identify non-responders, since a comprehensive evaluation of this cohort may result in better clinical outcomes [34,36].

Biomarker diagnostics

As was shown in multiple prospective randomized trials and in a recent study of almost 4,500 patients, CRT treatment has a clear overall benefit to suitable candidates [37]. However, we believe that after a successful implant, the emphasis should be on non-responders with potential for improvement (and not on responders), since appropriate (medical or invasive) intervention for non-responders may result in better quality of life and survival. Using the dynamic changes in NT-proBNP post-implantation may help in this respect. In our study, at 6-month follow-up, failure to achieve an NT-proBNP reduction of at least 25% was associated with non-response, using either echocardiography or clinical evaluation. It is well known that elevated NT-proBNP levels correlate with higher mortality in a heart failure population [38]. Using NT-proBNP change from baseline to 6 months post-implantation (during which time reverse remodeling has had a chance to take place) may be of incremental value in addition to baseline BNP levels and clinical data. The next step is therefore to investigate whether changes in proBNP alone can predict hard end points such as all-cause mortality and heart failure hospitalizations.

Limitations

This is a retrospective non-blinded single-center study with several limitations. Although all consecutive patients were invited to participate, there may have been a selection bias, since patients who chose to participate perhaps had fewer comorbidities (or differed in other respects) than patients who chose not to participate. A few patients were between NYHA class I and II at baseline, making the clinical response in those patients difficult to classify, (therefore we classified them as class and the true number of clinical responders may therefore have been underestimated. Age and renal function may have influenced the NT-proBNP level, although multivariate regression analysis was performed to correct for these factors. In some patients (mainly in the double responders group), no 6-month NT-proBNP was available for analysis. Data on LV electrode position and biventricular pacing percentage were not included in our analysis, although every effort was made to ensure ≥ 98% biventricular pacing. The implanting physicians targeted the LV lead placement in a lateral or posterolateral position with long electrical delay (measured as interlead RV-LV delay). The study outcome was based on 6-month clinical improvement or echocardiographic remodelling, and no longer-term mortality data were available for further investigation.

Conclusion

Our results were obtained from a non-randomized observational population outside the clinical trial setting. The results suggest that information on 6-month postoperative changes in NT-proBNP levels may help select responders vs. non-responders. The baseline level of this marker was not predictive; however, failure to achieve a reduction of the baseline NT-proBNP by ≥ 25% helped identify non-responders. NT-proBNP reduction after CRT-D implantation may be a useful additional tool to identify non-response. Our finding will require prospective testing in a randomized trial.

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