



ORIGINAL ARTICLE

Impact of cardiac resynchronization therapy on inflammatory biomarkers and cardiac remodeling: The paradox of functional and echocardiographic response



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KEYWORDS

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C-reactive protein

Abstract

Introduction: Response to cardiac resynchronization therapy (CRT) can currently be assessed by clinical or echocardiographic criteria, and there is no strong evidence supporting the use of one rather than the other. Reductions in B-type natriuretic peptide (BNP) and C-reactive protein (CRP) have been shown to be associated with CRT response. This study aims to assess variation in BNP and CRP six months after CRT and to correlate this variation with criteria of functional and echocardiographic response.

Methods: Patients undergoing CRT were prospectively enrolled between 2011 and 2014. CRT response was defined by echocardiography (15% reduction in left ventricular end-systolic volume) and by cardiopulmonary exercise testing (10% increase in peak oxygen consumption) from baseline to six months after device implantation.

Results: A total of 115 patients were enrolled (68.7% male, mean age 68.6 ± 10.5 years). Echocardiographic response was seen in 51.4% and 59.2% were functional responders. There was no statistical correlation between the two. Functional response was associated with a significantly greater reduction in BNP (-167.6 ± 264.1 vs. -24.9 ± 269.4 pg/ml; $p=0.044$) and CRP levels (-1.6 ± 4.4 vs. 2.4 ± 9.9 mg/l; $p=0.04$). Nonetheless, a non-significant reduction in BNP and CRP was observed in echocardiographic responders (BNP -144.7 ± 260.2 vs. -66.1 ± 538.2 pg/ml and CRP -7.1 ± 24.3 vs. 0.8 ± 10.3 mg/l; $p>0.05$).

Conclusion: An increase in exercise capacity after CRT implantation is associated with improvement in myocardial remodeling and inflammatory biomarkers. This finding highlights the importance of improvement in functional capacity after CRT implantation, not commonly considered a criterion of CRT response.

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PALAVRAS-CHAVE

Insuficiência cardíaca;
Terapia de ressincronização cardíaca;
Péptido natriurético tipo-B;
Proteína C-reativa

Impacto da ressincronização cardíaca nos biomarcadores inflamatórios e de remodelagem cardíaca**Resumo**

Introdução: A avaliação da resposta à terapêutica de ressincronização cardíaca (CRT) assenta em critérios clínicos e ecocardiográficos, sem evidência inequívoca que apoie o uso de uns em relação aos outros. Reduções do péptido natriurético tipo-B (BNP) e da proteína C-reativa (PCR) associaram-se à resposta à CRT. O objetivo deste estudo é avaliar a variação do BNP e PCR após seis meses de CRT e relacionar essa variação com critérios de resposta funcional e ecocardiográfica.

Métodos: De 2011 a 2014, doentes com indicação para CRT foram incluídos prospetivamente. A resposta à CRT foi definida por ecocardiograma (redução em 15% no volume telesistólico do ventrículo esquerdo) e por prova cardiorrespiratória (aumento de 10% no consumo de oxigénio máximo), aos seis meses.

Resultados: Foram incluídos 115 doentes (género masculino: 68,7%, idade média 68,6±10,5 anos); 51,4% apresentaram resposta ecocardiográfica e 59,2% resposta funcional. Não se verificou uma correlação estatisticamente significativa entre esses. Os respondedores funcionais apresentaram reduções estatisticamente significativas de BNP (-167,6±264,1 versus -24,9±269,4; p=0,044) e PCR (-1,6±4,4 versus 2,4±9,9; p=0,04). No grupo de respondedores ecocardiográficos essa redução não atingiu significância estatística [BNP (-144,7±260,2 versus -66,1±538,2) e PCR (-7,1±24,3 versus 0,8±10,3;p>0,05)].

Conclusão: Um aumento da capacidade funcional após implantação de CRT está associado a uma melhoria dos biomarcadores inflamatórios e de remodelagem reversa ventricular. Essa ideia enaltece a importância da melhoria da capacidade funcional após implantação de CRT, pouco considerada como critério de resposta à ressincronização.

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BNP	B-type natriuretic peptide
CHF	chronic heart failure
CPET	cardiopulmonary exercise testing
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
ICC	intraclass correlation coefficient
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
NYHA	New York Heart Association
VO ₂ max	peak oxygen uptake
VE/VCO ₂	minute ventilation-carbon dioxide production slope

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic chronic heart failure (CHF) and prolonged QRS despite optimal pharmacological therapy. By restoring the heart's electromechanical synchrony, CRT improves self-reported symptoms and reduces mortality and rehospitalization for heart failure.¹⁻⁴ Response to CRT is associated with left ventricular reverse remodeling, which is objectively assessed through echocardiographic parameters, particularly improvement in left ventricular ejection fraction (LVEF) and reduction in left

ventricular end-systolic volume (LVESV).⁵ Nonetheless, up to 40% of CRT recipients are considered non-responders.⁶ Improvement in New York Heart Association (NYHA) functional class and six-minute walk test distance have also been proposed as clinical response criteria in several studies.^{7,8} Improvement in peak oxygen uptake (VO₂ max), a marker of functional status and activity, has been described after CRT device implantation in a small cohort of patients.⁹ However, there is little agreement between the criteria of response, which suggests that clinical or functional improvement can occur without changes in echocardiographic parameters.¹⁰

B-type natriuretic peptide (BNP) is a marker of volume and pressure overload that has been proposed as a diagnostic and prognostic tool in CHF, in which it correlates well with severity. Moreover, pharmacological therapies that improve CHF symptoms and outcomes have been shown to reduce BNP levels.¹¹ Studies have also reported significant reductions in plasma BNP levels after CRT device implantation.¹²⁻¹⁴ Systemic inflammation is also known to play a role in CHF,¹⁵ and increased serum levels of inflammatory markers such as C-reactive protein (CRP) confer a dismal prognosis for CHF patients.^{16,17}

Nonetheless, there are conflicting data concerning reductions in BNP and CRP as markers of neurohormonal and inflammatory status after CRT device implantation.^{11,12} Moreover, their association with CRT response criteria that assess different pathological pathways of the syndrome is not fully understood.

Hence, this study aims primarily to assess variations in BNP and CRP six months after CRT device implantation, and secondarily to assess the association between changes in these laboratory variables and functional and echocardiographic response to CRT.

Methods

Population and study design

Between April 2011 and December 2014, consecutive patients referred for CRT device implantation in a tertiary center were systematically included in a prospective cohort study. Indications for CRT followed current international guidelines.¹⁸ All patients had been on optimal medical therapy for at least six months and were followed by a specialized heart failure team. A comprehensive assessment including demographic, clinical, laboratory, electrocardiographic, echocardiographic and cardiopulmonary exercise testing (CPET) was performed and data were collected at baseline and six months after device implantation and subsequently analyzed. The ethics committee of our university hospital center approved the study protocol and written consent was obtained for all patients.

Demographic and clinical data

Demographic and clinical data were obtained through medical consultation at baseline and at six-month follow-up. Demographic variables included age and gender. Clinical variables included heart failure etiology, classical cardiovascular risk factors, comorbidities, ongoing medication and NYHA functional class. A 12-lead electrocardiogram was also obtained to determine heart rhythm, QRS width and intraventricular conduction pattern.

Laboratory data

Blood samples were collected through peripheral venous catheterization into blood collection tubes with (serum) or without (plasma) anticoagulant (EDTA). All laboratory tests were performed after at least six hours fasting and at rest in a supine position in the same laboratory using hospital protocol, and assays were determined according to the manufacturer's recommendations. BNP was analyzed from plasma on a Spinchron DLX 800 (Beckman Coulter) centrifuge using a two-step chemiluminescence assay and serum CRP was determined with a nephelometer (Siemens BN ProSpecT).

Transthoracic echocardiography

A complete transthoracic echocardiogram was performed in all patients using a Vivid E9 scanner (GE Healthcare) with a 3 MHz probe, at baseline and at six-month follow-up. M-mode, two-dimensional, color, pulsed, continuous wave and tissue Doppler data were obtained from parasternal and apical views, and the standard echocardiographic parameters were calculated. Acquired cine-loop images with at least three cardiac cycles were analyzed offline (EchoPAC

software, GE Healthcare) for additional measures. LVEF, LVESV and left ventricular end-diastolic volume (LVEDV) were determined from apical 4- and 2-chamber views using Simpson's biplane method.¹⁹ The mean of three measurements was considered for analysis. Endocardial borders were manually traced and the left ventricular papillary muscles were included in volume acquisition. All measurements were reviewed by the same echocardiographic operator. The intraclass correlation coefficient (ICC) was calculated for LVESV to assess intraobserver variability. Echocardiographic response to CRT was established as a $\geq 15\%$ reduction in LVESV from baseline to six months after CRT device implantation, as previously published.²⁰

Cardiopulmonary exercise testing

CPET with ventilatory expired gas analysis was performed in all patients at baseline and at six-month follow-up using the modified Bruce protocol. Exercise test duration, VO_2 max and minute ventilation-carbon dioxide production slope (VE/VCO_2) were determined. A significant functional response to CRT was defined as a $\geq 10\%$ increase in VO_2 max from baseline to six-month follow-up.²¹

Cardiac resynchronization therapy device implantation

CRT device implantation was performed through a transvenous approach, using the subclavian and cephalic veins. The right atrial lead was positioned in the right atrial appendage and the right ventricular lead was actively fixed in the right ventricular apex or interventricular septum. The left ventricular lead was introduced using a long guiding sheath in order to cannulate the coronary sinus. An angiogram was performed and then the lead was positioned preferably in a lateral or posterolateral vein.

Statistical analysis

Baseline demographic and clinical data were expressed as means and standard deviation for continuous variables and as percentages for categorical variables. Changes in BNP and CRP (Δ BNP and Δ CRP) were established by the arithmetic subtraction of their values at six-month follow-up from baseline. Normality (Gaussian distribution) was tested in all continuous variables using the Shapiro-Wilk test. To assess the association between continuous variables, Pearson's or Spearman's correlation was used for normally or non-normally distributed data, respectively. Δ BNP and Δ CRP were separately compared between echocardiographic and functional responders and non-responders using the Student's t or Mann-Whitney tests for normally or non-normally distributed variables, respectively. The chi-square test was used to compare dichotomous variables. The level of significance considered was $\alpha=0.05$. Data were analyzed using SPSS for Windows, version 20.0 (IBM SPSS Inc, Chicago, IL).

Table 1 Baseline characteristics of echocardiographic and functional responders and non-responders.

Variables	LVESV \leq 15%			VO ₂ max \geq 10%		
	R (59)	NR (56)	p	R (68)	NR (47)	p
<i>Demographic</i>						
Age (years) (mean \pm SD)	68.5 \pm 14.3	66.5 \pm 8.3	NS	68.5 \pm 9.6	67.4 \pm 10.9	NS
Female (%)	30.6	29.4	NS	31	17.2	NS
<i>Clinical</i>						
Ischemic etiology (%)	16.7	29.4	NS	23.8	27.6	NS
AF (%)	20	23	NS	19	24	NS
NYHA II/III/IV (%)	31.4/62.9/2.9	21.9/75.0/3.1	NS	28.6/66.7/2.4	25.9/70.4/3.7	NS
Smoker (%)	13.9	11.8	NS	11.9	20.7	NS
Diabetes (%)	27.8	44.1	NS	33.3	41.4	NS
Hypertension (%)	75.0	70.6	NS	73.8	82.8	NS
Dyslipidemia (%)	61.1	55.9	NS	59.5	62.1	NS
Obesity (%)	27.8	20.6	NS	26.2	13.8	NS
Family history (%)	33.3	26.5	NS	33.3	31	NS
<i>Medication</i>						
Anticoagulants (%)	61.1	58.8	NS	59.5	58.6	NS
Beta-blockers (%)	69.4	76.5	NS	73.8	79.3	NS
ACEIs/ARBs (%)	80.6	73.5	NS	73.8	89.7	NS
Diuretics (%)	80.6	79.4	NS	83.3	79.3	NS
<i>Laboratory</i>						
CRP (mg/l) (mean \pm SD)	10.6 \pm 24.1	5.1 \pm 7.18	NS	4.55 \pm 5.3	3.0 \pm 3.6	NS
BNP (pg/ml) (mean \pm SD)	530.9 \pm 528.1	636.0 \pm 657.7	NS	520.7 \pm 439.7	404.3 \pm 485.1	NS
Cr (mg/dl) (mean \pm SD)	1.16 \pm 0.55	1.10 \pm 0.35	NS	1.07 \pm 0.67	1.15 \pm 0.83	NS
Hb (g/dl) (mean \pm SD)	12.1 \pm 0.87	11.8 \pm 0.79	NS	11.9 \pm 0.57	12.3 \pm 0.68	NS
<i>Electrocardiography</i>						
QRS width (ms) (mean \pm SD)	172.0 \pm 24.3	165.8 \pm 38.9	NS	166 \pm 25.7	176.6 \pm 25.1	
<i>Echocardiography</i>						
LVEF (%) (mean \pm SD)	24.8 \pm 6.5	26.3 \pm 7.7	NS	25.6 \pm 7.9	26.7 \pm 5.9	NS
LVEDV (ml) (mean \pm SD)	231.8 \pm 69.9	202.4 \pm 61.8	NS	225.6 \pm 68.7	218.5 \pm 84.0	NS
LVESV (ml) (mean \pm SD)	173.8 \pm 58.9	143.6 \pm 59.9	0.03	165.0 \pm 64.4	163.3 \pm 68.3	NS
<i>CPET</i>						
VO ₂ max (ml/min/kg)	15.1 \pm 6.6	23.0 \pm 15.4	NS	12.1 \pm 4.1	18.6 \pm 5.2	0.04
VE/VCO ₂ slope	38.9 \pm 9.9	61.7 \pm 37.4	NS	42.3 \pm 11.7	33.2 \pm 10.9	0.003
Duration (min)	3.63 \pm 2.62	3.8 \pm 2.5	NS	3.02 \pm 1.96	5.0 \pm 2.5	<0.001

ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; BNP: B-type natriuretic peptide; CPET: cardiopulmonary exercise test; Cr: creatinine; CRP: C-reactive protein; Hb: hemoglobin; NR: non-responder; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association functional class; R: responder; SD: standard deviation; VE/VCO₂: minute ventilation-carbon dioxide production slope; VO₂ max: peak oxygen consumption.

Results

Baseline characteristics

A total of 115 patients underwent CRT device implantation for whom complete data were collected at baseline and six-month follow-up. Mean age was 68.6 \pm 10.5 years and 68.7% were male. Ischemic heart failure etiology was reported in 29.1%. Mean QRS width at baseline was 172.1 \pm 28.8 ms and complete left bundle branch block was present in 56% of patients. Beta-blockers were prescribed in 86.2% of patients and 88.6% were treated with renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers). At

baseline, 74.3% patients were in NYHA functional class III or IV. Clinical improvement of at least one NYHA class was observed in 81.3% of patients. CRP and BNP presented a statistically significant reduction from baseline to six-month follow-up (CRP 7.0 \pm 15.6 to 6.5 \pm 15.3 mg/l, p <0.001, and BNP 533.6 \pm 553.6 to 404.9 \pm 530.3 pg/ml, p <0.001). Echocardiographic response was observed in 51.4% and functional response in 59.2%, assessed by the above criteria. Response as assessed by echocardiography was not statistically correlated with functional response (r =0.14, p =0.433 and chi-square=0.063, p =0.80).

Table 1 delineates the baseline demographic and clinical characteristics of responders and non-responders assessed by both sets of criteria independently. Table 2 details

Table 2 Laboratory, electrocardiographic, echocardiographic and cardiopulmonary exercise test data at baseline and six-month follow-up.

	Baseline	Six-month follow-up	p
<i>Laboratory</i>			
CRP (mg/l) (mean ± SD)	7.0 ± 15.6	6.5 ± 15.3	p<0.001
BNP (pg/ml) (mean ± SD)	533.6 ± 553.6	404.9 ± 530.3	p<0.001
<i>Electrocardiography</i>			
QRS width (ms) (mean ± SD)	172.1 ± 28.8	169.4 ± 13.5	p<0.001
<i>Echocardiography</i>			
LVEF (%) (mean ± SD)	26.4 ± 7.0	38.7 ± 11.2	p<0.001
LVEDV (ml) (mean ± SD)	208.6 ± 69.5	201.3 ± 81.6	p<0.001
LVESV (ml) (mean ± SD)	158.1 ± 57.7	140.4 ± 66.1	p<0.001
<i>CPET</i>			
VO ₂ max (ml/min/kg)	16.4 ± 4.11	14.5 ± 5.2	p<0.001
VE/VCO ₂ slope	38.0 ± 11.6	32.4 ± 7.1	p<0.001
Duration (min)	3.7 ± 2.4	4.7 ± 2.2	p<0.001

BNP: B-type natriuretic peptide; CPET: cardiopulmonary exercise testing; CRP: C-reactive protein; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; VE/VCO₂: minute ventilation-carbon dioxide production slope; VO₂ max: peak oxygen consumption.

laboratory, echocardiographic and CPET data at baseline and at six-month follow-up.

Echocardiographic response

In our cohort, severely reduced mean LVEF at baseline was observed (26.4±7.0%). A significant improvement in mean LVEF and reduction in mean LVEDV and LVESV were noted after CRT device implantation. Additionally, 63.4% of patients showed more than 10% improvement in LVEF and in 51.4% of patients LVESV decreased by more than 15% compared to baseline (echocardiographic responders). An ICC of 0.89 at baseline and 0.87 at six-month follow-up was calculated for intraobserver variability of LVESV. BNP reduction was more pronounced in responders than in non-responders as assessed by echocardiography, although this did not achieve statistical significance (-144.7±260.2 vs. -66.1±538.2 pg/ml, p>0.05) (Figure 1). Echocardiographic responders also presented a non-significant reduction in serum CRP levels after CRT (-7.1±24.3 vs. 0.7±10.3 mg/l, p>0.05) (Figure 2).

Functional response

VO₂ max during CPET was severely depressed at baseline (mean 14.5±5.2 ml/min/kg). However, a statistically significant improvement (14.5±5.2 to 16.4±4.1 ml/min/kg, p<0.001) was observed after CRT device implantation. Improvement in exercise capacity was also shown by a significant reduction in VE/VCO₂ slope and longer CPET duration (38.0±11.6 vs. 32.4±7.1 and 3.7±2.4 vs. 4.7±2.2 ms, respectively, all p<0.001) at six-month follow-up. BNP reduction was significantly more pronounced in those classified as functional responders (-167.6±264.1 pg/ml vs. -24.9±269.4 pg/ml, p=0.044) (Figure 3). CRP reduction was seen in functional responders, while non-responders presented elevation in mean CRP levels six months after CRT

device implantation (-1.6±4.4 vs. 2.4±9.9 mg/l, p=0.040) (Figure 4). A significant reduction in VE/VCO₂ slope was also noted in functional responders (-9.8±10.5 vs. 1.9±7.2, p=0.001).

Discussion

In our study population a significant reduction of CRP and BNP was observed six months after CRT (CRP 7.0±15.6 to 6.5±15.3 mg/l, p<0.001 and BNP 533.6±553.6 to 404.9±530.3 pg/ml, p<0.001). The CRP and BNP reductions were significantly higher in the functional responder group, whereas they did not achieve statistical significance in the echocardiographic responder group.

Heart failure is a systemic condition with increased levels of natriuretic peptides and inflammatory markers.^{12,13} Therapies targeting these pathways have shown positive prognostic impact in this syndrome.^{11,17}

As described, our cohort represents a severe heart failure population characterized by poor self-reported functional status, reduced exercise capacity and low mean LVEF. Moreover, compared to other studies, our population presented a higher proportion of nonischemic heart failure etiology, such as idiopathic, valvular and alcoholic, only 29.1% of patients having ischemic heart failure.¹⁸ The heart failure etiology did not significantly differ between functional or echocardiographic responders and non-responders. Patients in our population presented advanced age, which excludes them from a heart transplantation program, and they were already on optimal medical therapy. Additionally, the high mean BNP and CRP levels presented at baseline support the concept of an advanced heart failure population, and significant reductions in BNP and CRP levels were observed at six-month follow-up after CRT device implantation, which is in line with previous studies.^{22-24,12}

Response to CRT is the subject of considerable debate, since there is no established definition for therapeutic

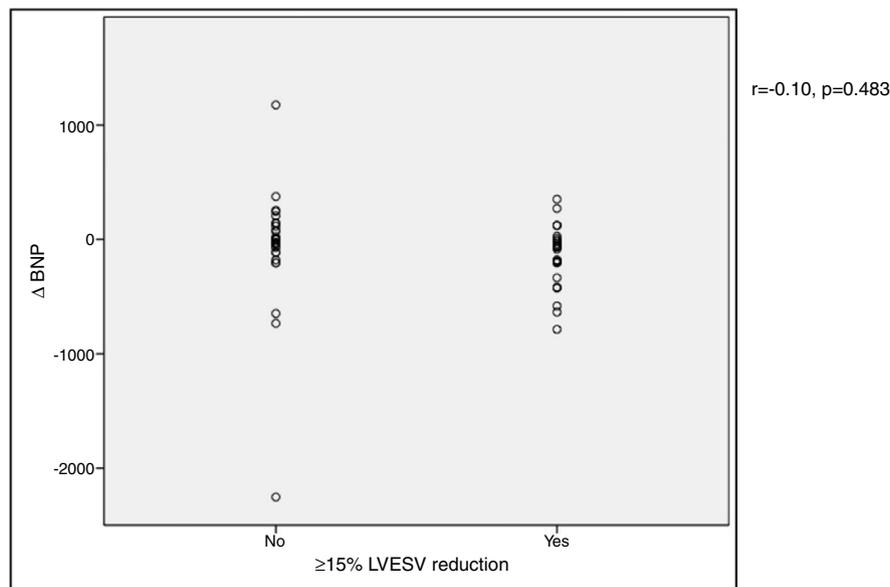


Figure 1 Correlation between B-type natriuretic peptide (BNP) levels and echocardiographic response to cardiac resynchronization therapy. Response was defined as a $\geq 15\%$ reduction in left ventricular end-systolic volume (LVESV). Δ BNP: variation in BNP levels.

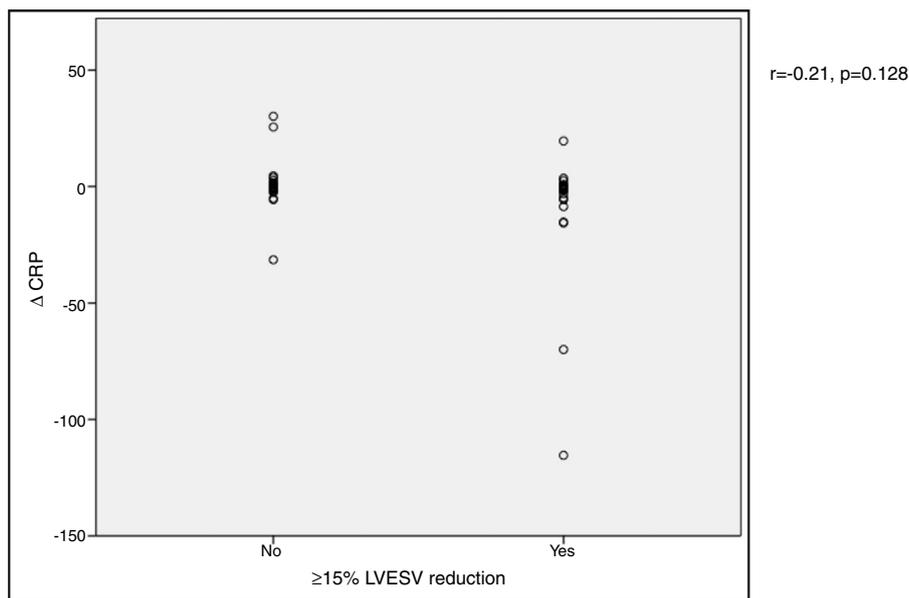


Figure 2 Correlation between C-reactive protein (CRP) levels and echocardiographic response to cardiac resynchronization therapy. Response was defined as a $\geq 15\%$ decrease in left ventricular end-systolic volume (LVESV). Δ CRP: variation in CRP levels.

response.²⁰ Improvement in LVEF and reductions in LVESV and LVEDV are the result of left ventricular reverse remodeling. Pharmacological therapies targeting this effect have been shown to be associated with better long-term outcomes in heart failure patients.^{25–28} The cut-off of a $\geq 15\%$ reduction in LVESV has been described as a more specific surrogate of left ventricular reverse remodeling than LVEF, and has been used to define those responding to CRT therapy by echocardiography.^{10,11,14,21} In our study, only 51.4% of patients achieved this demanding criterion at six months. These echocardiographic responders had a more pronounced reduction in BNP at six-month follow-up than non-responders, but this did not achieve statistical

significance. Despite targeting the same mechanism, the demanding cut-off for LVESV reduction, the short follow-up time for structural changes and variability in BNP could explain this phenomenon. Regarding the changes in CRP, a widely used marker of systemic inflammation, there was no significant association with reduced LVESV, perhaps because they reflect different pathways of the pathological disease process. The association reported in the literature between reduced LVESV and changes in BNP or CRP after CRT has in fact been variable.^{14,28,29}

Exercise capacity, measured through VO_2 max during CPET, is known to be a major prognostic indicator in heart failure patients.^{30,31} It has been assessed in conjunction with

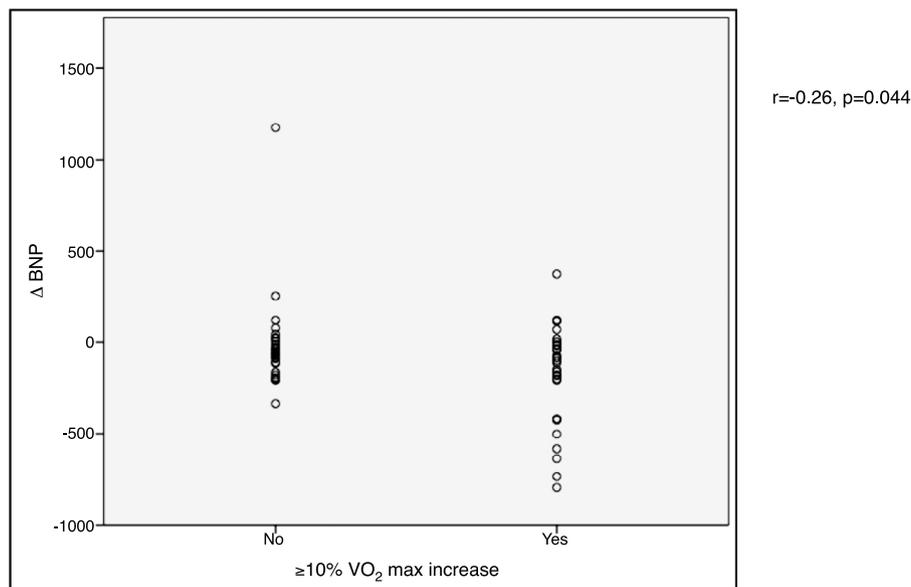


Figure 3 Correlation between B-type natriuretic peptide (BNP) levels and functional response to cardiac resynchronization therapy. Response was defined as a $\geq 10\%$ increase in peak oxygen consumption (VO_2 max). Δ BNP: variation in BNP levels.

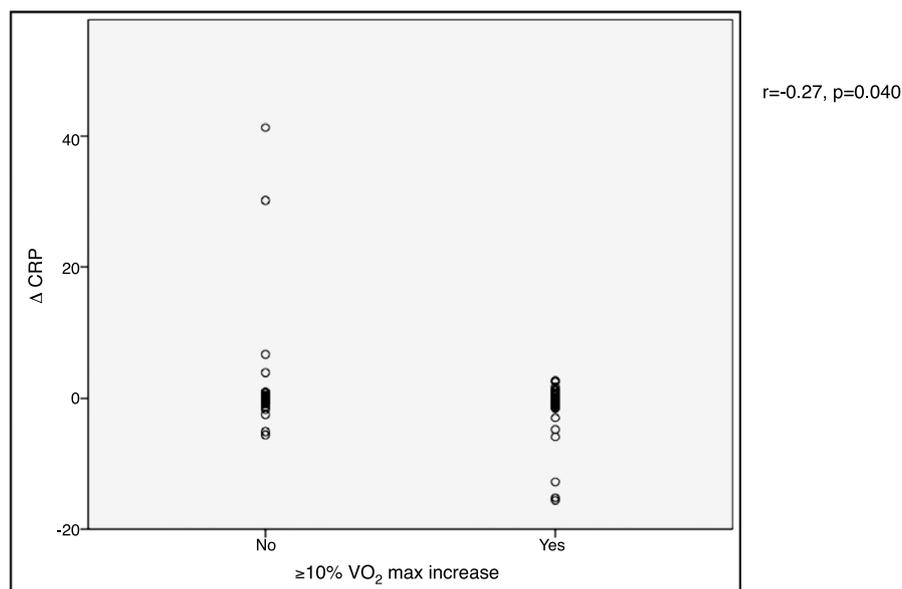


Figure 4 Correlation between C-reactive protein (CRP) levels and functional response to cardiac resynchronization therapy. Response was defined as a $\geq 10\%$ increase in peak oxygen consumption (VO_2 max). Δ CRP: variation in CRP levels.

pharmacological therapies for heart failure patients.³² However, its use for determining functional response after CRT is not routinely considered and lacks clinical evidence. We used a cut-off of $\geq 10\%$ improvement in VO_2 max to define functional responders, and our study revealed significantly greater reductions in BNP and CRP among CRT patients in whom VO_2 max improved substantially at six-month follow-up. An association between reductions in neurohormonal and inflammatory levels and a $\geq 10\%$ improvement in VO_2 max has not previously been reported in this population. Volume overload in heart failure is responsible for raised left ventricular and atrial pressure and consequently elevation of pulmonary capillary wedge pressure, which is

associated with functional exercise impairment.¹³ Moreover, systemic inflammatory markers increase oxygen demand, depress myocardial function and disturb homeostasis in the pulmonary vasculature, influencing the interaction between heart and lungs.³³ This finding suggests that electromechanical resynchronization may have a role in reversing these pathological processes, which highlights the importance of considering improvement in VO_2 max after CRT as a response criterion.

In our study, the association between reduced LVESV and improved VO_2 max was non-significant, suggesting that those who improved by one criterion may not have improved by the other. Similarly, Fornwalt et al. showed that agreement

between criteria of clinical, echocardiographic and functional exercise response after CRT device implantation is poor,¹¹ indicating that CRT may lead to improvements in different parameters in different patients. Functional response supported by reduction in BNP and CRP could be related to CRT response independently of significant left ventricular reverse remodeling at six-month follow-up.

Study limitations

Follow-up time in this study was set at six months after CRT implantation, which may be insufficient to assess the long-term structural changes of left ventricular reverse remodeling. Moreover, inferences cannot be made about the lasting clinical, laboratory or echocardiographic alterations in this population after this time. Additionally, CRP levels are susceptible to variability, and ongoing inflammatory processes that influenced CRP levels cannot be excluded.

Conclusion

CRT was associated with important reductions in BNP and CRP levels at six-month follow-up. Patients presenting significantly improved functional capacity, considered functional responders, showed significant reductions in serum BNP and CRP levels at six-month follow-up, reflecting its benefit on ventricular remodeling and inflammation. In echocardiographic responders this effect was smaller and non-significant, which calls attention to the importance of assessing functional response in CRT patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation*. 2009;119:969–77.
2. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834–43.
3. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med*. 2004;141:381–90.
4. Wells G, Parkash R, Healey JS, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *Cann Med Assoc J*. 2011;183:421–9.
5. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. *Circulation*. 2010;122:985–92.
6. Zhang Q, Zhou Y, Yu C-M. Incidence, definition, diagnosis, and management of the cardiac resynchronization therapy nonresponder. *Curr Opin Cardiol*. 2015;30:40–9.
7. Wessler BS, Kramer DG, Kelly JL, et al. Drug and device effects on peak oxygen consumption, 6-minute walk distance, and natriuretic peptides as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. *Circ Heart Fail*. 2011;4:578–88.
8. De Marco T, Wolfel E, Feldman AM, et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. *J Card Fail*. 2008;14:9–18.
9. Larsen AI, Lindal S, Myreng K, et al. Cardiac resynchronization therapy improves minute ventilation/carbon dioxide production slope and skeletal muscle capillary density without reversal of skeletal muscle pathology or inflammation. *Europace*. 2013;15:857–64.
10. Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. *Circulation*. 2010;121:1985–91.
11. Brouwers C, Versteeg H, Meine M, et al. Association between brain natriuretic peptide, markers of inflammation and the objective and subjective response to cardiac resynchronization therapy. *Brain Behav Immun*. 2014;40:211–8.
12. Glick A, Michowitz Y, Keren G, et al. Neurohormonal and inflammatory markers as predictors of short-term outcome in patients with heart failure and cardiac resynchronization therapy. *Isr Med Assoc J*. 2006;8:391–5.
13. Tarquini R, Guerra CT, Porciani MC, et al. Effects of cardiac resynchronization therapy on systemic inflammation and neurohormonal pathways in heart failure. *Cardiol J*. 2009;16:545–52.
14. Galrinho A, Branco LM, Oliveira MM, et al. Cardiac resynchronization therapy – clinical and echocardiographic characteristics of responders and exceptional responders. *Rev Port Cardiol*. 2009;28:959–69.
15. Araújo JP, Lourenço P, Azevedo A, et al. Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. *J Card Fail*. 2009;15:256–66.
16. Kamioka M, Suzuki H, Yamada S, et al. High sensitivity C-reactive protein predicts nonresponders and cardiac deaths in severe heart failure patients after CRT implantation. *Int Heart J*. 2012;53:306–12.
17. Kavsak PA, MacRae AR, Newman AM, et al. Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. *Clin Biochem*. 2007;40:326–9.
18. Developed in collaboration with the European Heart Rhythm Association (EHRA). 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2281–329.
19. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–67.
20. Foley PWX, Leyva F, Frenneaux MP. What is treatment success in cardiac resynchronization therapy? *Europace*. 2009;11 Suppl. 5:v58–65.
21. António N, Teixeira R, Lourenço C, et al. Which echocardiographic definition should be used to define response to cardiac resynchronization therapy? *Rev Port Cardiol*. 2009;28:943–58.
22. Balci KG, Balci MM, Sen F, et al. The role of baseline indirect inflammatory markers in prediction of response to cardiac resynchronization therapy. *Kardiol Pol*. 2016;74:119–26.
23. Theodorakis GN, Flevari P, Kroupis C, et al. Antiinflammatory effects of cardiac resynchronization therapy in patients with chronic heart failure. *Pacing Clin Electrophysiol*. 2006;29:255–61.

24. Hoogslag GE, Höke U, Thijssen J, et al. Clinical, echocardiographic, and neurohormonal response to cardiac resynchronization therapy: are they interchangeable? *Pacing Clin Electrophysiol.* 2013;36:1391–401.
25. Yu CM, Bleeker GB, Fung JW-H, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation.* 2005;112:1580–6.
26. Reis JR de AR, Cardoso JN, Cardoso CM dos R, et al. Reverse cardiac remodeling: a marker of better prognosis in heart failure. *Arq Bras Cardiol.* 2015;104:502–6.
27. Bertini M, Höke U, van Bommel RJ, et al. Impact of clinical and echocardiographic response to cardiac resynchronization therapy on long-term survival. *Eur Heart J Cardiovasc Imaging.* 2013;14:774–81.
28. Cattadori G, Giraldi F, Berti M, et al. Assessment of cardiac resynchronization therapy response. *Int J Cardiol.* 2009;136:240–2.
29. Lappegård KT, Bjørnstad H. Anti-inflammatory effect of cardiac resynchronization therapy. *Pacing Clin Electrophysiol.* 2006;29:753–8.
30. Cicoira M, Davos CH, Francis DP, et al. Prediction of mortality in chronic heart failure from peak oxygen consumption adjusted for either body weight or lean tissue. *J Card Fail.* 2004;10:421–6.
31. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. *J Heart Lung Transplant.* 2006;25:1024–42.
32. Frankenstein L, Nelles M, Hallerbach M, et al. Prognostic impact of peakVO₂-changes in stable CHF on chronic beta-blocker treatment. *Int J Cardiol.* 2007;122:125–30.
33. Rubaj A, Ruciński P, Oleszczak K, et al. Inflammatory activation following interruption of long-term cardiac resynchronization therapy. *Heart Vessels.* 2013;28:583–8.