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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

Heart failure;  
Cardiac resynchronization therapy;  
B-type natriuretic peptide;  
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  $68.6 \pm 10.5$  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 ( $-167.6 \pm 264.1$  vs.  $-24.9 \pm 269.4$  pg/ml;  $p=0.044$ ) and CRP levels ( $-1.6 \pm 4.4$  vs.  $2.4 \pm 9.9$  mg/l;  $p=0.04$ ). Nonetheless, a non-significant reduction in BNP and CRP was observed in echocardiographic responders (BNP  $-144.7 \pm 260.2$  vs.  $-66.1 \pm 538.2$  pg/ml and CRP  $-7.1 \pm 24.3$  vs.  $0.8 \pm 10.3$  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 <sub>2</sub> max	peak oxygen uptake
VE/VCO <sub>2</sub>	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.<sup>1-4</sup> 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).<sup>5</sup> Nonetheless, up to 40% of CRT recipients are considered non-responders.<sup>6</sup> 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.<sup>7,8</sup> Improvement in peak oxygen uptake (VO<sub>2</sub> max), a marker of functional status and activity, has been described after CRT device implantation in a small cohort of patients.<sup>9</sup> However, there is little agreement between the criteria of response, which suggests that clinical or functional improvement can occur without changes in echocardiographic parameters.<sup>10</sup>

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.<sup>11</sup> Studies have also reported significant reductions in plasma BNP levels after CRT device implantation.<sup>12-14</sup> Systemic inflammation is also known to play a role in CHF,<sup>15</sup> and increased serum levels of inflammatory markers such as C-reactive protein (CRP) confer a dismal prognosis for CHF patients.<sup>16,17</sup>

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

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