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REVIEW ARTICLE

Prognostic Significance of Biomarkers of Inflammation and Myocardial Fibrosis in Assessing Response to Cardiac Resynchronization Therapy

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Abstract

A significant proportion of patients undergoing cardiac resynchronization therapy (CRT) fail to respond despite standard selection criteria. This review examines the prognostic value of biomarkers related to myocardial stress (NT-proBNP), fibrosis (galectin-3, sST2), and inflammation (hsCRP, TNF-α, IL-6) in predicting CRT outcomes. NT-proBNP remains the most reliable marker, with reductions post-CRT indicating favorable response. Elevated levels of sST2 and galectin-3 are linked to adverse events and non-response. Integrating these biomarkers into clinical scoring systems may enhance patient stratification, though variability and lack of standardization remain challenges.

Keywords: Cardiac Resynchronization Therapy, Biomarkers, Natriuretic Peptide, Brain, Galectin 3

Introduction

To date, despite the significant development of instrumental methods to assess the efficacy of cardiac resynchronization therapy (CRT), the problem of patients not responding to therapy, even when selected with all generally accepted selection criteria, remains high.

In addition, patients scheduled for SRT may have a number of comorbidities such as metabolic syndrome, diabetes mellitus, chronic kidney disease, etc. that influence the clinical outcome of SRT results [7; 24].

In this regard, biomarkers have received special attention [2]:

Myocardial stress or myocardial dysfunction (BNP (brain natriuretic peptide); NT-proBNP (N-terminal probrain natriuretic peptide)

Fibrosis and remodeling of extracellular matrix (galectin-3 - gal-3; sST2 - suppression of tumorigenicity 2; soluble tumorigenicity suppressor receptor type 2);

Inflammation (high-sensitivity C-reactive protein, hsCRP; tumor necrosis factor-α, TNF-α); pro-inflammatory cytokines (interleukin-1, IL-1 and IL-6)

As a rule, BNP and NUP levels in blood are usually very low, but are significantly increased in patients with CH [12]. Liquori M. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"19 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] found that atrial dilatation and ventricular wall tension stimulate the synthesis and release of BNP.

The correlation of which with both clinical and structural parameters in CH has been noted by a number of researchers. This will make it possible to clarify the classification of response to CRT and improve prognosis at early stages [24].

NT-proBNP is considered as a "gold standard" in the diagnosis of CHF with a high class of evidence in a number of clinical guidelines. Clear threshold values of BNP and NT-proBNP levels in blood for diagnosis of chronic and acute decompensation of CH, regardless of LVEF, have been determined. BNP ≥35 pg/mL and NT-proBNP ≥125 pg/mL are considered significant for the diagnosis of CHF [1; 20].

The CARE-HF study included 813 patients with the longest follow-up period and showed a significant correlation between NUP levels and long-term CRT outcome. In addition, changes in NUP levels over time are associated with morbidity and mortality [6].

Direct correlation between NT-proBNP level and Ea/Es (r=0.50; p=0.0001) and negative correlation with LV EF (r=-0.45; p=0.003) was revealed in patients with CHF II-III FC [3].

Hoogslag G. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"15 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] studied the relationship between NT-proBNP changes 6 months after CRT and clinical and echocardiographic responses, as well as the relationship between NT-proBNP changes and long-term outcome. After 6 months of follow-up, improvement in NYHA class ≥1 point, reduction in CSR ≥15%, and NT-proBNP ≥15%. A reduction in NT-proBNP ≥15% showed better concordance with echocardiographic (71%) response compared with clinical (58%) response.

The aim of the BIOCRT study [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"26 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] was to investigate the biomarkers of CH in the coronary sinus (CS) or initial peripheral veins (PV) in the cross-section of response to CRT. NT-proBNP concentrations >2000 pg/mL, galectin-3 (gal-3) concentrations >25.9 ng/mL, and sST2 concentrations >35 ng/mL were considered the cut-off point for PVs.NT-proBNP concentrations were 20% higher in the CC than in PVs, whereas gal-3 and sST2 concentrations were 10% higher in the periphery than in PVs (all $p < 0.001$).

After 6 months, 45% had not responded to SRT and 16 (22%) patients experienced serious adverse cardiovascular events (including death, heart transplantation, left ventricular assist device placement, and hospitalization for heart failure within 2 years) [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"26 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"].

In conclusion, assessment of BNP or NT-proBNP levels before SRT or in the following months may be a marker for predicting patients with poor response who may benefit from more aggressive medical treatment.

Shlevkov N.B. et al. [4] studied neurohormones NT-proBN and sST2 as predictors of SRT-D response and established their threshold values NT-proBNP <3900 pg/mL and sST2 <50 ng/mL. The authors believe that sST2 is a universal marker of patient response to SRT-D.

According to the results of the MADIT-CRT study [21], sST2 elevation was an independent predictor of the combined endpoint. After 1 year, a 10% increase in sST2 concentration was associated with an 11% increase in the risk of cardiac death or development of sustained VT/PEF.

In the HF-ACTION study [5], which analyzed the prognostic value of cardiac biomarkers of myocardial stress (NT-proBNP), inflammation and fibrosis (sST2 and gal-3). It is noted that high values of all three markers correlated with the risk of death from the progression of CHF.

High gal-3 values were associated with response to SRT at 6 months and with cardiovascular outcome at 48 months. In the CARE-HF subanalysis, gal-3 was an independent predictor of death from any cause or unplanned hospitalization [5; 8].

Cai C. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"11 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] found that baseline levels of high-sensitivity CRP (hsCRP) can serve as a prognostic marker of the risk of death or hospitalization in patients with CH. Decreased or maintained low levels of hsCRP were observed in responders to SRT. According to the authors, determination of hsCRP levels before and after CRT can provide information that will help in determining the clinical management strategy of CRT recipients.

According to Kamioka M. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"16 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"], responders had significantly higher hsCRP levels than non-responders. The cutoff point of hsCRP >3.0 mg/L has been proposed for predicting cardiac mortality.

Brouwers C. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"10 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] found no difference in the levels of CRP, IL-6, TNF-α, sTNFr1 and sTNFr1 between responders and nonresponders to SRT. However, in SRT responders, TNF-α levels remained low over time.

Despite many years of experience in the use and high efficacy of SRT, the principles of patient selection for SRT are still debated and there is a lack of consistency among researchers in assessing response to SRT

Heist E. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"14 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] decided to investigate whether the evaluation system, which includes combined patient selection parameters and immediate hemodynamic response, would improve the prediction of response to SRT. The hemodynamic effect of SRT was determined using Doppler analysis of mitral regurgitation as the percentage change in maximal +dP/dt (DeltadP/dt) with SRT on versus off. Acute response to SRT was defined as Deltadp/dt ≥25%.

In the study, the authors concluded there was a significant association between response score (0 to 4 points) and acute hemodynamic response to SRT ($p < 0.0001$), i.e., a higher response score was associated with improved survival after SRT ($p = 0.0019$).

Theuns D. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"25 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] evaluated the influence of comorbidities using the modified Charlson comorbidity index (CCI) in 463 patients with CH who underwent CRT-D to predict primary or secondary

prevention of sudden cardiac death. Age-adjusted CHI≥5 (very severe comorbidities) was found to be a predictor of mortality in SRT-D recipients.

The MADIT-SRT study created a risk assessment scale that included the most significant clinical risk factors affecting mortality in SRT-D: female sex, NCMP, presence of BLNPG, QRS, previous hospitalizations for CH and CSR ≥125 ml/$m^2$and left atrial volume <40 ml/$m^{(2)}$[13 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"]

Levy W. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"18 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] developed the Seattle Heart Failure Model (SHFM) model and web calculator, which can predict 1-, 2-, and 3-year survival using routine clinical, pharmacologic, instrumentation, and laboratory parameters. The SHFM can be used to effectively stratify patients with CH on SRT/SRT-D and provide adequate discrimination of the risk of mortality from any cause.

Park J. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"23 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] proposed 6 Echocardiographic parameters including LV end-diastolic size, LV global function index, LV diastolic function (LV area), LV size (LV end-diastolic area index) and LV systolic and diastolic function (LV area) as predictors of response after CRT, which can predict reverse LV remodeling.

Kang Y. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"17 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] developed a grading system based on clinical, ECG, and ECHO parameters to select patients for SRT. A 4-point grading system was established based on tricuspid annulus systolic excursion (TAPSE), longitudinal strain, and complete BLNPH combined with wide QRS.

For quantitative assessment of dyssynchrony and efficiency of patient selection for SRT implantation, Orszulak M. et al. [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"22 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"] proposed the Regional Strain Performance Index (RSPI), which takes into account dyssynchrony in 12 regions (three apical projections with four segments in each projection).

The range of survival prediction systems for CRT that use routine laboratory and clinical parameters is very broad: EAARN, VALID-CRT, HF-CRT, CRT-SCORE, AL-FINE, ScREEN, CRT-D Futility score, MAGGIC [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"9 HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634673/"].

Today, more and more researchers are using new approaches to analyze clinical and instrumental data using artificial intelligence and machine learning to develop a model to predict response to SRT and identify candidates for therapy.

Thus, despite the significantly increased number of different systems for assessing the response to SRT, there is a marked heterogeneity. This fact significantly complicates their implementation in clinical practice.

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