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REVIEW ARTICLE

Usefulness of Biomarkers for Predicting Response to Cardiac Resynchronization Therapy

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Abstract: Cardiac Resynchronization Therapy (CRT) is an effective treatment strategy for heart failure. It significantly improves clinical symptoms and decreases mortality and long-term morbidity. However, some patients do not respond properly to this treatment. In this review, the role of different biomarkers in predicting response to CRT is discussed. Some biomarkers, including natriuretic peptides and inflammatory markers have promising results but further trials are needed for more evaluation.

***Methods*:** All the studies reporting the extent of biomarkers for predicting the response to cardiac resynchronization therapy were included in this study. For studies using the same database, the ones with a higher number of cases and more complete data were included. Conclusions were drawn from relevant randomized controlled clinical trials and meta-analyses about CRT implantation and its associated alterations in biomarker levels. Cardiac Resynchronization in Heart Failure (CARE-HF) study was the first and the largest study on patients with CRT with the longest follow-up, which showed a significant correlation between BNP levels and long-term CRT outcome. CRP has been demonstrated to be a mediator of inflammation and a marker indicating the presence of an inflammatory process.

***Conclusion*:** Natriuretic peptides, including BNP, markers of collagen synthesis like PINP, inflammatory markers, especially CRP, gal-3, and CT-apelin yield promising results in left ventricular remodeling and their relationship with response to CRT implantation is seen. Although more research is needed in this area as little information is available for baseline and preprocedural measurements, so that it would be easy to choose appropriate candidates for CRT implantation.

Keywords: Heart failure, CRT, biomarkers, natriuretic peptides, electrocardiography, inflammatory markers.

1. INTRODUCTION

Heart Failure (HF) is a complex clinical syndrome with structural and hemodynamic abnormalities. In addition to available medical treatments, Cardiac Resynchronization Therapy (CRT) has become an effective treatment strategy for patients with HF. CRT is indicated for patients with an ejection fraction of 35% or less, Left Bundle Branch Block (LBBB) conduction delay in electrocardiography, and New York Heart Association (NYHA) class II to IV despite medical treatment, and not all patients with heart failure. There are two types of CRT devices: CRT Pacemakers (CRT-P), and a combination of CRT pacemakers and defibrillation therapy (CRT-D). Since the introduction of CRT more than 20 years ago, its role in HF has been well established and discussed in several studies [1-3]. Both devices improve symptoms (New York Heart Association (NYHA) class), exercise tolerance (6-minute walk distance), and improve quality of life scores by decreasing dyssynchrony in patients with advanced chronic HF [4]. CRT optimizes the cardiac output, pulse pressure, and left ventricular dp/dt [5]. Moreover, it decreases Pulmonary Artery Pressure (PAP) and Pulmonary Capillary Wedge Pressure (PCWP) [6]. It also reduces the degree of mitral regurgitation, leading to LV reverse remodeling [7]. Some studies have also shown decreased re-hospitalization in patients undergoing CRT implantation. In general, CRT implantation significantly improves clinical symptoms and decreases mortality and long-term morbidity, and thereby it has become an accepted treatment modality in HF patients [8].

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Despite these benefits, approximately one-third of the patients do not respond to this treatment [9]. On the other hand, according to epidemiological studies, HF is a leading cause of morbidity and mortality in the United States with 50% mortality in 5 years, which underlines the importance of treatment in these patients [10]. Moreover, CRT is a costly therapy and thus patients and caregivers should be provided with realistic expectations on its prognosis. Thus, predicting the response to CRT implantation is of great value. Currently, the precise process of reverse LV remodeling following CRT implantation is not completely understood. Therefore, there is no definite marker to predict who would benefit from CRT implantation.

During recent years, there has been a growing interest in identifying new markers for diagnosing cardiac dysfunction, evaluating response to treatment for dyssynchronous contractions, and optimizing device programming. To the best of our knowledge, although a large body of literature has defined the role of a wide spectrum of markers, there is no comprehensive review of them. Accordingly, this study was conducted to review various biomarkers that have been proposed to correlate with clinical response to CRT implantation.

2. METHODS

2.1. Search Strategy

A comprehensive search of MEDLINE, Embase, Cochrane Library, Cochrane Collaboration, and Cochrane Database of Systematic Reviews (CDSR) was conducted in December 2018. The keywords selected for our search were a combination of MeSH (Medical Subject Headings) terms of the National Library of Medicine, which are used to index articles for PubMed, and the following key-terms were "Cardiac Failure, Heart Decompensation, Right-Sided Heart Failure, Myocardial Failure, Congestive Heart Failure, Left-Sided Heart Failure, Cardiac Resynchronization Therapy, Cardiac Resynchronization Pacing Therapy, Cardiac Resynchronization, Atrio-Biventricular Pacing, Biventricular Pacing, Biomarker, Biologic Marker, Biological Marker, Laboratory Marker, Serum Marker, Surrogate Endpoints, Clinical Marker, Biochemical Marker, and Immunologic Marker". All these peer-reviewed publications in these databases were included for screening. There was no date/language limit for this literature search. Only studies in the full-text format were included. The reference lists of the relevant articles were also manually reviewed and entered in the screening phase in order to retain any relevant study. Search terms were expanded to take into account spelling differences of keywords between American and British English.

2.2. Study Selection

The retrieved studies were imported in the Endnote software and the duplicates were removed. Two reviewers independently screened the titles and abstracts of the studies with each record reviewed by two independent reviewers. After obtaining the full text of eligible papers, two reviewers independently reviewed them for inclusion and exclusion criteria. Any discrepancy regarding the eligibility of studies was resolved by the third reviewer.

2.3. Inclusion and Exclusion Criteria

All the studies reporting the extent of biomarkers for predicting the response to cardiac resynchronization therapy were included in this study. In order to avoid misleading data, we only included case series when they reported at least 10 cases and excluded all the case reports. In articles that described the outcomes of all patients undergoing CRT implantation, only the data of patients with HF were obtained for the review. For studies using the same database, we included the one with a higher number of cases and a more complete data. We reviewed relevant randomized controlled clinical trials and meta-analyses to obtain conclusions about CRT implantation and its associated alterations in biomarker levels. When these types of studies were not available, relevant case-control, cross-sectional and case series that employed appropriate methodologies were reviewed. Only studies without follow-up data were excluded.

2.4. Assessment of Methodological Quality

As this is a narrative review, we did not conduct a quality assessment and used no checklists for appraising the included full-texts.

3. REVIEW OF LITERATURE

3.1. Natriuretic Peptides

Natriuretic Peptides (NP) are a group of neurohormones that have several roles; they have natriuretic and diuretic properties and reduce angiotensin II and norepinephrine synthesis, leading to vasodilation [11]. Atrial dilation and ventricular wall stress have been proved to stimulate BNP synthesis and release [12]. In the last decade, BNP has been proposed as a strong independent prognostic marker in HF patients irrespective of the underlying cardiovascular disease [13]. In addition, changes in BNP level over time are associated with morbidity and mortality [14].

The underlying mechanism of response to CRT implantation remains unclear. However, previous studies showed that myocardial Troponin C (TNC) activates Matrix Metalloproteinase (MMPs), including MMP-9, *via* Transforming Growth Factor (TGF)-β. A study [15] found that BNP could increase MMP production, especially MMP-9. On the other hand, Marleen *et al.* [16] reported a reduction in TNC, MMP-9, and N-terminal pro-Brain Natriuretic peptide (NT-proBNP) levels in CRT responders while they found no changes in the MMP-2 level. They proposed that CRT reduced myocardial TNC and permitted reverse LV remodeling, leading to decreased cardiomyocyte slippage and improved cardiac function.

Cardiac Resynchronization in Heart Failure (CARE-HF) [17] study was the first and the largest study on patients with CRT with the longest follow-up, which showed a significant correlation between BNP levels and long-term CRT outcome.

In one study [18], subjective (*e.g.* NYHA class) and objective parameters (*e.g.* QRS complex duration and morphology in ECG, quality of life score, six-minute walking distance, left ventricular ejection fraction or LVEF, severity of mitral regurgitation, dyssynchrony within the left ventri-

cle, and BNP) were used for evaluation of response to CRT-P implantation. The results showed a reduction in plasma BNP concentrations with an improvement in the clinical status. Thus, it was suggested that natriuretic peptides were useful objective and quantitative markers for the evaluation of response to CRT implantation. Moreover, these markers were suggested to be of greater prognostic value *vs.* diagnostic value. This is consistent with a study [19] conducted in 2013 which also found that objective evaluation of CRT response was more accurate than subjective methods such as clinical assessment and reported a stronger correlation between reduced NT-proBNP and echocardiographic findings of the CRT response compared to the reduction of these markers and clinical response (70% *vs.* 58%). In another study [20], patients with HF who had NYHA class III and a QRS duration of 195 ms underwent CRT implantation. Unlike other studies, pharmacotherapy remained stable during the first 3 months of follow-up. The plasma level of BNP was evaluated before and after 3 months of implantation. This study suggested the percentage of BNP level change as a more powerful predictor of the long-term benefits of CRT implantation compared to NYHA class, conventional echocardiographic parameters, and cardiopulmonary exercise testing at 3 months of follow-up.

Friedrich *et al.* [21] investigated the effect of CRT implantation on the plasma concentration of NT-proBNP. They found that the median plasma concentration of NT-proBNP was relatively similar in patients receiving CRT or medical therapy at baseline, (1920 pg/mL and 1809 pg/mL, respectively) while it significantly decreased in patients receiving CRT at 3 months (537 pg/mL; $p<0.0001$) and 18 months (567 pg/mL; $p<0.0001$) of follow-up. They concluded that CRT caused an early and sustained reduction of NT-proBNP by improving the ventricular function and therefore this marker could be used as a simple tool for CRT response monitoring. In this regard, Lellouche *et al.* introduced the BNP level as a marker of CRT response in HF patients with NYHA class III or IV [22]. They suggested a BNP cut-off value of 447 pg/ml with a sensitivity and specificity of 62% and 79%, respectively.

In a recent cohort study [23], NT-proBNP was measured at baseline and six months after CRT implantation. It was found that the sixth month NT-proBNP levels, unlike baseline levels, were significant indicators of non-responders to CRT implantation. It was also suggested that a simple biomarker measurement during follow-up might help to identify non-responders who have poor outcomes after CRT implantation. Although high BNP levels after CRT implantation showed non-responders, the role of measuring serum BNP before CRT implantation to predict responders was not discussed. In a study [24] of patients with LVEF < 40% and a QRS duration of >120 milliseconds in the form of bundle branch block or intraventricular conduction delay undergoing CRT-P implantation, NT-proBNP levels were measured at baseline as well as 1 and 3 months after treatment. A correlation was found between the reduced NT-proBNP levels and the degree of LV reverse remodeling, increased LVEF, and maximum exercise capacity. Furthermore, a positive regression was observed between the amount of decrease in BNP level and clinical status improvement, response to LV reverse remodeling, and better long-term clinical outcome (lower mortality, or mortality and cardiovascular hospitalization). For patients who had less significant changes in NT-proBNP levels after 3 months, other treatments such as the placement of pacing leads and more aggressive medical therapy regimens were suggested.

In agreement with this, Filzmaier *et al.* [25] found significant reductions in BNP levels after only 4-6 days of continuous biventricular pacing. Another retrospective study [26] of end-stage. HF patients showed that BNP levels measured during the early period after CRT implantation were a significant predictor of long-term clinical outcomes. A limitation of this study was its small sample size. The suggested prognostic role of BNP was indicated early after CRT implantation in this study while other studies showed the long-term prognostic value of BNP. In this regard, it was concluded that BNP could be used as a parameter to facilitate an early diagnosis of non-responders to CRT so that advanced treatments such as cardiac transplantation or mechanical circulatory support could be implemented for the survival of patients. A cohort study [27] of 1197 patients with baseline BNP data enrolled in MADIT (Multicenter Automated Defibrillator Implantation Trial)-CRT, despite the need for further support for baseline and follow-up BNP assessment, suggested that monitoring BNP levels after CRT implantation could be used to improve risk assessment in mildly symptomatic HF (NYHA class I and II) patients.

In a BIOCRT study [28] in 2014, which is the largest CRT cohort reported with simultaneous Coronary Sinus (CS) and Peripheral Vein (PV) blood sampling obtained during device implantation, 45% of the patients were CRT non-responders at 6 months and 22% experienced major adverse cardiovascular events including death, cardiac transplant, left ventricular assist device, and HF hospitalization at 2 years. Despite the need for larger studies to confirm these findings, the authors suggested that CS sampling of HF biomarkers might be better than PV sampling for predicting CRT outcomes. It was noted that biomarkers were not static and were greatly dependent on the patient's HF status on the sampling day. As a result, serial pre and postoperative sampling were suggested.

In conclusion, it seems that checking BNP or NT-proBNP levels on the day of CRT implantation or in the following months can be useful in predicting poor responders who may benefit from more aggressive medical treatments. However, there is not enough evidence supporting the evaluation of baseline plasma natriuretic peptides in CRT candidates in order to decide who would benefit from CRT implantation.

3.2. Markers of Neurohormonal Activation

Decreased neurohormonal activation during medical treatment of heart failure is associated with hemodynamic and clinical improvement. Georgette *et al.* found that patients with neurohormonal responses had a better long-term outcome compared to non-responder patients [19].

Arginine Vasopressin (AVP) is a peptide hormone synthesized in the hypothalamus and stored in the posterior pituitary gland with both antidiuretic and vasoconstrictive properties [12]. Levels of AVP have been shown to be elevated in patients with HF. In the BACH study [29], high levels of AVP were associated with increased 90-day mortal-

ity, HF-related visits at the emergency department, and HF hospitalizations. Copeptin is another neurohormonal biomarker. Stoiser *et al.* found that copeptin was a stronger predictor of death than BNP, but BNP was a better predictor of HF hospitalization [30]. Neuhold *et al.* demonstrated that co-peptin correlated with the NYHA class and confirmed that co-peptin was superior to BNP and NT-proBNP for predicting of mortality [31].

No study has investigated AVP or co-peptin in CRT implantation. By contrast, one study [32] found no significant changes in epinephrine, norepinephrine, and aldosterone, so-called neurohormones, in HF patients before and after CRT implantation. In another study [20], a significant decrease was observed in the plasma levels of big Endothelin-1 (ET-1) and BNP after three months of CRT implantation, which predicted improvement in clinical status at 12 and 24 months of follow-up.

3.3. Markers of Fibrosis and Extracellular Matrix Remodeling

3.3.1. Procollagen

Collagen scar formation plays an important role in myocardial remodeling and HF development. For this reason, as a non-invasive evaluation method, markers of collagen synthesis, especially procollagen type I (PINP) and type III (PIIINP) amino-terminal propeptide, as well as the markers of collagen degradation including carboxy-terminal telopeptide of collagen type I (CITP) are the most studied markers to determine the extent of cardiac fibrosis.

In a recent study [33], LVEF, PIIINP, and NT-proBNP levels were of the most to the least significant additive value in predicting mortality and response to CRT implantation. In this study, a positive echocardiographic response was associated with low levels of circulating PIIINP and long-term survival in CRT recipients.

In another study [34], serum PINP and CITP were measured in heart failure patients at baseline and 1 year after CRT implantation. The patients were categorized as responders or non-responders by objective methods. The results showed that the PINP to CITP ratio was higher at baseline compared to post-therapy measurements among responders while the PINP to CITP ratio remained unchanged in non-responders. Interestingly, prior to CRT implantation, the PINP to CITP ratio was similar in both responder and non-responder groups. This study suggested a cut-off value of 14.4 for the PINP to CITP ratio for predicting response to CRT implantation with a relative risk of 2.07 (70% specificity, 63% sensitivity, 95% confidence interval = 0.98-4.39).

Similarly, in a study [35] conducted in 2016, PINP and CITP were measured before and after 6 months of CRT implantation in HF patients. The comparison of responders and non-responders showed no significant differences in PINP and CITP at baseline. At the sixth month of follow-up, no significant changes were observed in CITP levels ($p>0.05$) between the two groups. However, the serum PINP level was higher in responders *vs*. non-responders, indicating that collagen synthesis increased in responders in the first 6 months after CRT implantation. Moreover, it is of value to note that a similar study [36] in patients undergoing Left Ventricular Assist Device (LVAD) implantation showed a significant increase in PINP and PIIINP levels in the first 200 days after implantation.

A study [37] found that serum PINP and PIIINP levels increased during follow-up in responders to CRT implantation whereas they remained unchanged in non-responders. In this study, responders had significantly lower serum PINP levels at baseline compared to non-responders (32.9 *vs*. 41.8 μg/L; $p<0.05$). By contrast, serum CITP levels did not change, although they tended to be higher in responders versus non-responders at baseline (3.54 *vs*. 2.08 μg/L, p = non-significant). It was concluded that reverse LV remodeling following CRT implantation was associated with an increased collagen synthesis rate in the first 6 months of follow-up.

In contrast to the above, one study [38] found that the baseline PIIINP, rather than other biomarkers, was lower in CRT responders than in non-responders (0.80 *vs*. 0.96 μg/L, $p = 0.03$). Less elevated plasma PIIINP levels in HF patients indicated a lesser amount of cardiac fibrosis and a favorable response to CRT and served as an independent biomarker for predicting a better response to CRT implantation (odds ratio = 0.20, 95% CI = 0.03-1.17, $p = 0.07$). In support of this result, a randomized clinical trial [39] conducted in 2011 found that Extracellular Cardiac Matrix (ECCM) biomarkers and NT-proBNP could not predict response to CRT implantation and suggested that cardiac fibrosis was not a major determinant of cardiac dyssynchrony.

The results of a recent systematic review [40] of ECM biomarkers in predicting response following CRT showed that N-terminal propeptides of type I and III procollagens expression demonstrated a replicated ability to predict reverse left ventricular remodeling.

A recent study [41] discussed the potential use of biomarkers for predicting the need for additional ICD in potential CRT recipients. The authors reported that multiple prospective randomized controlled trials were conducted to evaluate the efficacy of CRT in improving the patients' medical condition but also added that most of these studies used a CRT device combined with an ICD (CRT-D). They concluded that due to current literature and the best available evidence, implementing ICD, with or without CRT, in patients with heart failure, LVEF ≤ 35 %, and NYHA II/IV is recommended.

In conclusion, it seems that the markers of collagen synthesis like PINP have a degree of correlation with response to CRT implantation, which may be a result of changes in left ventricular remodeling. However, more evidence is needed to draw a stronger conclusion. Previous studies did not measure baseline collagen markers before CRT implantation for decision-making. Furthermore, another limitation indicates that only a few fibrosis biomarkers have been associated with histological and documented fibrosis, which reduces the robustness of such biomarkers and the related conclusions.

3.3.2. Galectin-3

Galectin-3 (gal-3), a β-galactosidase binding lectin, is expressed and secreted by macrophages [42]. It can bind to

cell surface receptors, antigens, and extracellular matrix glycans, and is associated with activation of fibroblasts and macrophages. Several studies found a correlation between gal-3 and cardiovascular outcomes [42]. The results of these studies suggest that high levels of gal-3 lead to the progression of HF and are associated with a worse prognosis [42].

According to a large cohort study [28] of HF patients undergoing CRT implementation whose CS and PV blood samples were matched, the NT-proBNP level was 20% higher in the CS than the periphery, while both gal-3 and sST2 levels were 10% higher in the periphery than CS (all $p < 0.001$). It was shown that unlike NT-proBNP, gal-3 and sST2 were synthesized peripherally in response to HF. The study suggested the use of triple markers (NT-proBNP, gal-3, and sST2) from CS (with 95% specificity) to predict CRT non-responders instead of using any single marker (all $p <0.01$). Using CS gal-3 as a single marker had a specificity of 90% in this regard ($p = 0.50$) [28]. The development of major adverse cardiovascular events in HF patients undergoing CRT implementation (defined as the composite endpoint of death, cardiac transplant, left ventricular assist device, and HF hospitalization at 2 years) could not be predicted using any single or multiple biomarker strategies. However, determining dual CS gal-3 and sST2 was associated with identifying high-risk patients for developing such adverse events [28].

According to the CARE-HF study [39], gal-3 > 30 ng/mL along with left ventricular end-systolic volume > 200 mL (3.42 (OR: 1.65-7.10), $p = 0.001$) is associated with death or HF hospitalization (OR (95% CI): 2.98 (1.43-6.22), $p = 0.004$). Some recent studies reported that a lower cut point of plasma gal-3 was associated with death or HF hospitalization by using the same ELISA method. De Boer *et al.*, for instance, reported an association between Gal-3 ≥ 20 ng/mL and death or HF hospitalization in patients hospitalized for acute decompensated HF with or without a low LVEF [43]. Shah *et al.* reported even lower levels of gal-3 (Gal-3 ≥ 15 ng/mL) in a similar study population [44].

In the MADIT study [45], the correlation of gal-3 and HF, baseline gal-3 levels was measured. The results showed that lower baseline gal-3 levels in patients prior to CRT implementation were associated with a greater reduction in the risk of the primary endpoint. In addition, a 65% *vs.* 25% decrease was observed in patients with a gal-3 level in the top quartile of the distribution *vs.* lower baseline measurements. (a higher baseline value was associated with a hazard ratio (HR) of 0.35, 95% CI 0.19-0.67 and a lower baseline value was associated with a HR of 0.75, 95% CI. 0.51-1.11). It was concluded that elevated galectin-3 level was an independent predictor of adverse HF outcomes in patients with mildly symptomatic HF. (multivariable-adjusted HR per log unit: 1.55; 95% CI 1.01-2.38; $p = 0.043$).

In conclusion, available data suggest that the baseline gal-3 level and its levels in the follow-up period can predict a lack of response to CRT implantation. However, such trials are scarce, and larger studies are needed to clarify and establish the role of this marker in response prediction.

3.4. Markers of Inflammation

3.4.1. CRP

Since the 1990s, measuring the C Reactive Protein (CRP) level has opened new insights into the role of inflammation in a variety of cardiovascular pathophysiologies. CRP has been demonstrated to be a mediator of inflammation and a marker indicating the presence of an inflammatory process [46].

In a study [47] conducted in 2012 with the purpose of determining the predictive role of high sensitive CRP (hsCRP) in responders to CRT implantation, hsCRP was significantly higher in non- responders compared to the responders ($p<0.01$) with an independent multivariate logistic relationship between the hs-CRP level and the lack of response to CRT implantation (OR:1.499, $p = 0.011$). Rather than being a response predictor, the hsCRP level has been reported to be the strongest predictor of cardiac death (HR: 1.337. $p = 0.001$). In this regard, a cut-off point of > 3.0 mg /L for hsCRP has been suggested for cardiac mortality.

In another study [48] in 2006, the levels of hsCRP and BNP decreased significantly 2 weeks after CRT implantation (BNP mean difference was 229.1 ± 102.5 pg/ml, $p < 0.0001$; hsCRP mean difference was 5.2 ± 2.4 mg/dl, $p = 0.001$). The results showed that CRT reduced inflammatory axis activation in patients with advanced HF by decreasing peripheral levels of hsCRP. However, no correlation was found between the clinical outcomes and the baseline levels of hsCRP or its post-procedural levels. An early decrease in the levels of BNP and hsCRP was generally observed in HF patients treated with CRT in this study.

3.4.2. Tumor Necrosis Factor-α (TNF-α)

Although the prognostic role of TNF-α as a marker for HF has been well established, whether TNF-α directly contributes to the progression of HF or is a simple marker of disease severity is still unclear. There are studies suggesting different effects for TNF-α; in the early phase, TNF-α appears to have a mild inotropic effect while it becomes a cardio-depressant factor in the long term [49].

Markers of inflammation including CRP, interleukin-6 (IL-6), TNF-α, soluble TNF receptor (sTNFr) 1 and 2 were measured in a study [50]. There was no difference in CRP, IL6, TNF-α, sTNFr1 and sTNFr1 levels between objective (based QRS duration, LVEF, *etc.*) CRT-responders *vs*. non-responders over time. However, subjective (based on NYHA class, *etc.*) CRT-responders showed significantly lower levels of TNF-α over time compared to the non-responders.

The plasma levels of TNF-α and IL-6 were assessed in a study [51] conducted in 2014. The proportion of ≥15% decrease in left ventricular end-systolic volume in response to CRT was 70%, 42%, and 33% according to the lower, intermediate, and upper third of TNF-α distribution, respectively ($p = 0.01$). By contrast, a study suggested that CRT was unable to counteract the inflammatory mediators despite its beneficial effects on symptoms and remodeling [32].

3.4.3. Other Pro-inflammatory Markers

Plasma interleukin (IL)-6, epidermal growth factor, fibroblast growth factor (FGF)-2, IL-1a, IL-1b, IL-4, and IL-13 were evaluated in a study [52] conducted in 2016. It was determined that detectable reparative cytokine IL-13 was significantly associated with freedom from heart failure hospitalization or death and more than 15% decrease in echocardiographic end-systolic volume at 12 months (odds ratio 3.79, $p<0.0001$). By contrast, detectable pro-inflammatory/ fibrotic growth factor FGF-2 was negatively associated with freedom from heart failure hospitalization or death (odds ratio 0.31, $p<0.004$).

3.5. Markers of Cardiomyocyte Injury

Cardiotrophin-1 (CT-1), a member of the interleukin family [53], is a dose-dependent inducer of eccentric hypertrophy rather than concentric hypertrophy [54] and is elevated in experimental congestive heart failure [55]. According to a study [56], it is not clear if CT-1 plays an active role in the pathophysiological mechanisms of ventricular remodeling and heart failure progression. However, a significant decrease in CT-1 plasma levels has been found in CRT responders. By contrast, it has been shown that patients with cardiac events at follow-up have higher CT-1 plasma levels.

4. OTHER MARKERS

4.1. CT-apelin

Apelin, an endogenous ligand for the G protein-coupled apelin receptor, is emerging as an important regulator of the cardiovascular homeostasis. Chong *et al.* found that plasma apelin was significantly lower in patients with advanced heart failure referred for heart transplantation [57]. In another study of 80 patients, the level of circulating apelin increased in early stages while it decreased to a lower level in advanced heart failure although it remained in the normal plasma range [58].

In one study [59], serum CT-apelin significantly decreased in responders (from 549.5 ng/ml to 211.0 ng/ml; $p < 0.0001$) at six months while it remained unchanged in non-responder patients (from 472.5 ng/ml to 541.0 ng/ml; $p = 0.80$). In this cohort study, the odds ratio of non-response was 10 times higher in patients with high serum CT-apelin levels while higher NT-proBNP levels increased the odds of non-response by 16 times [59]. However, multivariate ROC testing suggested the superiority of CT-apelin over NT-proBNP (CT-apelin: AUC 0.78; 95%CI: 0.59-0.97; $p = 0.013$ versus NT-proBNP: AUC 0.67; 95% CI: 0.49-0.85; $p = 0.13$) that was also confirmed in multivariate logistic regression analysis (CT-apelin: $p = 0.01$, NT-proBNP: $p = 0.41$).

4.2. β1-AAbs and M2-Aabs

A study [60] was conducted to evaluate the role of autoantibodies specific for the β1-adrenergic (β1-AAbs) and muscarinic (M2-AAbs) receptors in patients with chronic HF of various etiologies and several findings undergoing CRT implantation. Unlike M2-AAbs, a significantly higher percentage of patients who were positive for β1-AAbs (OD sample/OD reference ratio >2.1) was observed in non-responders compared to the responders (57% *vs.* 27%, $p = 0.004$). Therefore, this study concluded that the evaluation of β1-AAb was useful for predicting poor CRT-D response and identifying responders to CRT-D. Moreover, the presence of β1-AAbs correlated with elevated renal function parameters.

4.3. Annexin A5

The correlation of CRT-induced LV reverse remodeling with a reduction in plasma Anexin A5 (AnxA5) was investigated in a study [61]. It was concluded that the beneficial effects of CRT were related to decreased AnxA5 levels.

4.4. Endothelial Progenitor Cells (EPCs)

EPCs, a highly heterogeneous population of stem cells, have the capacity to proliferate and differentiate into mature endothelial cells, contributing *in vivo* to both re-endothelialization and neoangiogenesis. EPCs increase in patients with endothelial damage and reflect increased endothelial cell turnover in HF patients [62]. Therefore, measurement of EPCs levels can be used as a predictor to identify the subset of HF patients who are more likely to undergo reverse remodeling and benefit from CRT implantation.

4.5. MicroRNA-30d

MicroRNAs (miRNAs) regulate gene networks and play an important role in cardiovascular fibrosis, atherosclerosis, and arrhythmias [63]. They are implicated in the pathogenesis of HF [64], are present in extracellular vesicles, and have emerged as biomarkers of cardiovascular disease [65]. In a pilot study [66], baseline plasma miR-30d levels were associated with response to CRT in HF patients. An increase in cardiomyocytes MiR-30d correlates with areas of increased wall stress in HF and is protective against deleterious tumor necrosis factor signaling. A recent prospective pilot study [67] of 52 patients evaluated the panel of miRNAs (miRNA-21, miRNA-30d, miRNA-122, miRNA-133a, miRNA-210, and miRNA-486) beside NT-pro-BNP, NT-pro-peptides of collagen I and III, collagen I CTx, MMP-2, and MMP-9 in HF patients undergoing CRT. No specific biomarkers reached significance for predicting functional response to CRT.

4.6. Osteopontin

Upregulation of Osteopontin (OPN), a newly identified determinant of ECM turnover and composition, leads to excess fibroblast proliferation and ECM formation accompanying ventricular dysfunction [68]. A study [69] found a significant correlation ($r = -0.56$; $p = 0.01$) between relative changes of LVESV and plasma OPN. It was indicated that circulating OPN might represent a marker of LV dilation/impairment and could be used as an indicator of response to HF therapies promoting LV reverse remodeling.

CONCLUSION

Several biomarkers have been investigated for their role in left ventricular remodeling and their relationship with response to CRT implantation. Promising results were observed for natriuretic peptides including BNP, markers of collagen synthesis like PINP, inflammatory markers especially CRP, gal-3, and CT-apelin. A small body of evidence supports the role of annexin A5 and β1-AAbs. Some other markers like osteopontin, microRNA-30d, and EPCs are related to remodeling but no sound trial is available to assess their predictive role following CRT implantation, and there is still a gap of knowledge in this regard. First, the number of studies investigating each marker is limited and more information is needed to establish their impact. Second, most available trials show the effect of postprocedural marker measurement on short-term or long-term follow-up outcomes and little information is available for baseline and preprocedural measurements. Thus, currently, these markers have no role in decision making to choose appropriate candidates for CRT implantation. Third, it seems that a multimarker strategy may be of more predictive value in identifying CRT responders, which can be a subject for future trials.

CONSENT FOR PUBLICATION

Not applicable.

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