Markers of Cardiac Resynchronization Therapy

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Abstract

Despite the well-recognized benefits of CRT, an unsolved problem is the fact that based on the current selection criteria up to 30 % of patients do not respond to this therapy. Therefore, it is of paramount importance to try to identify more precisely patients who will derive the best benefit of this invasive therapy. Patient selection for CRT should involve a multimodal approach, and new promising tools may help in this difficult process. In this chapter, we will briefly discuss the impact of CRT in the expression of several biomarkers and also their role as predictors of CRT response, namely endothelial progenitor cells, brain natriuretic peptide, inflammatory mediators, biological markers, and renal function.

Keywords

Heart failure • Cardiac resynchronization therapy • Predictors of response • Inflammatory mediators • Endothelial progenitor cells • BNP • Renal function

Abbreviation

BNP	Brain natriuretic peptide
CKD	Chronic kidney disease
CRT	Cardiac resynchronization therapy
EPCs	Endothelial Progenitor Cells
GFR	glomerular Filtration Rate
HF	Heart Failure
hs-CRP	high sensitivity C Reactive Protein
ICTP	carboxyterminal telopeptide of type I collagen
LV	Left Ventricular
LVESV	left ventricular end-systolic volume
MDRD	Modification of Diet in Renal Disease
NYHA	New York Heart Association
NT- proBNP	terminal fragment pro-brain natriuretic peptide
NP	Natriuretic peptides
HF	Heart Failure
TNFα	Tumor Necrosis Factor α

Introduction

The normal functioning of the heart depends on the sequential activation of its components throughout the cardiac cycle, which requires the integrity of the electrical conduction system. The term *ventricular dyssynchrony* refers to the altered timing and pattern of ventricular contraction due to electrical disturbances or distorted electrochemical substrate, which might compromise the pumping capacity of the heart. These disorders are common in patients with heart failure, in particular when there are disturbances in the conduction system, such as bundle branch blocks.

The ventricular conduction delays produce suboptimal ventricular filling, reduction in left ventricular contractility, increased mitral regurgitation, and abnormal septal wall motion, thus affecting the performance of an already dysfunctional heart (Abraham 2015; Dickstein et al. 2010; Daubert et al. 2012; Brignole et al. 2013).

The electrocardiographic definition of ventricular dyssynchrony consists in an increased duration of the QRS complex (above 120 milliseconds) in the surface electrocardiogram, reflecting delayed ventricular activation. One-third of patients with systolic heart failure meet these criteria, and nowadays it is possible to treat this disturbance with pacing devices (cardiac resynchronization therapy – CRT). In brief, a pacing lead is implanted in the coronary sinus to pace the left ventricle, and another lead is placed in the right ventricle, thus improving the synchrony of ventricular activation. There is an increased stroke volume of the left ventricle after this therapy; the chronic benefits include left ventricle reverse remodeling with a reduction in left ventricular end-systolic and end-diastolic volumes, which is associated with an improvement in ejection fraction. Furthermore, tackling dyssynchrony significantly improves left ventricular mechanics with reduction of functional mitral regurgitation (Abraham 2015; Dickstein et al. 2010; Daubert et al. 2012; Brignole et al. 2013).

CRT has been studied in symptomatic patients with depressed ejection fraction and electrocardiographic criteria of ventricular dyssynchrony in several randomized controlled trials (MUSTIC, MIRACLE, MIRACLE ICD, CONTAK CD, CARE-HF, COMPANION, MADIT-CRT, REVERSE, and RAFT trials) (Linde et al. 2002; Abraham et al. 2002; Young et al. 2003; Achtelik et al. 2000; Cleland et al. 2005; Bristow et al. 2004; Moss et al. 2009; Linde et al. 2008; Tang et al. 2010). Overall, CRT improves symptoms and exercise tolerance, reduces heart failure hospitalization by 50 %, and diminishes mortality by 35 %. Based on these studies, CRT with biventricular pacing is recommended in symptomatic patients (NYHA functional class II, III, or IV) on optimal medical treatment with reduced left ventricular ejection fraction ($\leq$35 %) and prolonged QRS duration (above 120 milliseconds if left bundle branch block morphology, above 150 milliseconds if other morphologies) (Dickstein et al. 2010; Brignole et al. 2013).

Despite the formal recommendations and overall benefits of CRT, there are some unresolved issues. First, the implantation of both leads is technically feasible in 88–92 % of the procedures and carries a small risk of coronary sinus lesion, thus hindering some patients from its benefits. Secondly, around 30 % of the patients with biventricular pacing do not respond to this therapy (Dickstein et al. 2010; Brignole et al. 2013).

Several criteria have been proposed to define CRT response. Some entail clinical measures, such as symptomatic functional class improvement, reduced hospitalizations, and superior quality of life; these are subjective and prone to placebo effect. Echocardiographic criteria are more objective, namely increased ejection fraction and reduced left ventricular end-diastolic volume, the latter a marker of reverse remodeling. Considering the plethora of response criteria, up to 50 % of patients are classified as nonresponders. Since CRT is expensive and is not without hazard, it seems sensible to try to identify more precisely those who will derive the best benefit

and those least likely to, as in this latter group the cost-effective equation will be dramatically different (Yu and Hayes 2013; Yu et al. 2010).

There are subgroups of patients who show better response to CRT: female gender, those with wider QRS duration, left bundle branch block morphology, nonischemic heart failure etiology, and without significant scarred myocardium. Some authors have explored the role of several imaging techniques in predicting response to CRT, but the results have been disappointing. Therefore, it is of paramount importance to identify better predictors of CRT response (Yu CM, Hayes DL 2013; Yu CM et al. 2010).

Apart from the mechanical dyssynchrony effect of CRT, there is growing data on the "reverse cellular remodelling" following effective biventricular pacing. Some studies compared changes in cellular signaling pathways by CRT in responders versus "nonresponders," showing that myocardial gene expression changes of calcium handling proteins and natriuretic peptides were reversed preferentially in responders. Moreover, successful CRT is associated with decreased circulating biomarkers of extracellular matrix remodeling, such as tenascin-C and matrix metalloproteinase 9, and anti-inflammatory effects with reduced chemoattractant protein-1, interleukin-8, and interleukin-6 levels. Patients with effective CRT display chronic enhancement of circulating apelin, a secreted hormone that can block adverse remodeling and has positive inotropic effects (Cho et al. 2012).

The knowledge of the mechanisms involved in reverse cellular remodeling response has led to its application in CRT response prediction. For instance, studies using a metabolomic approach concluded that altered free fatty acid flux and calculated maximal adenosine triphosphate synthesis could be used to predict nonresponse to CRT, due to impaired energy efficiency. Likewise, several biomarkers are being studied in their abilities to predict CRT response (Barth et al. 2012).

In this chapter, we will explore the impact of CRT in the expression of several biomarkers and also their role as predictors of CRT response, namely endothelial progenitor cells, brain natriuretic peptide, inflammatory mediators, biological markers, and renal function.

Cardiac Resynchronization Therapy and BNP/NT-proBNP

Despite treatment with angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists, morbidity and mortality remains high in patients with chronic heart failure. The prognosis is even worse in patients with HF who have prolonged QRS intervals. This may reflect cardiac dyssynchrony and a greater propensity to adverse ventricular remodeling Fruhwald et al. 2007.

CRT with or without a defibrillator has been shown in several large randomized controlled trials to be effective at reducing symptoms, hospitalization time, and mortality in HF patients. However, despite its success in large studies, a lack

of response to CRT has been reported in up to one-third of device recipients Brenyon et al. 2013.

The issue of CRT "response" remains controversial. There is no good definition of a "responder" or "nonresponder." The fact that a patient's symptoms may not have improved, or the left ventricular volumes have not reduced, is used by many to indicate lack of response, but such an approach ignores the fact that patients may have had a mortality benefit, or might (without device) have deteriorated further. Approximately 70 % of patients who undergo CRT feel better. However, there is a large placebo response to CRT as demonstrated in MIRACLE group McDonagh et al. 2011.

Several factors, including high BNP levels, have been proposed as predictors of poor response to CRT.

Some patients respond spectacularly well to CRT and some deteriorate. A subanalysis of the PROSPECT study defined super-responders as having a reduction in left ventricular end-systolic volume (LVESV) of 30 % or more, responders a reduction of 15–29 %, nonresponders a reduction of 0–14 %, and "negative responders" an increase in LVESV. Super-responders were more frequently female, had nonischemic HF, a wider QRS complex, and more extensive dyssynchrony at baseline. The reported percentages of clinical responders and non- responders are shown in Fig. 1.

While it is important to identify patients who are most likely to respond to CRT, it is perhaps more important to identify patients in whom CRT may actually be harmful; in that way, BNP and NT-proBNP have been suggested to be a useful tool in both pre-CRT risk stratification and in monitoring for post-CRT response Brenyon et al. 2013.

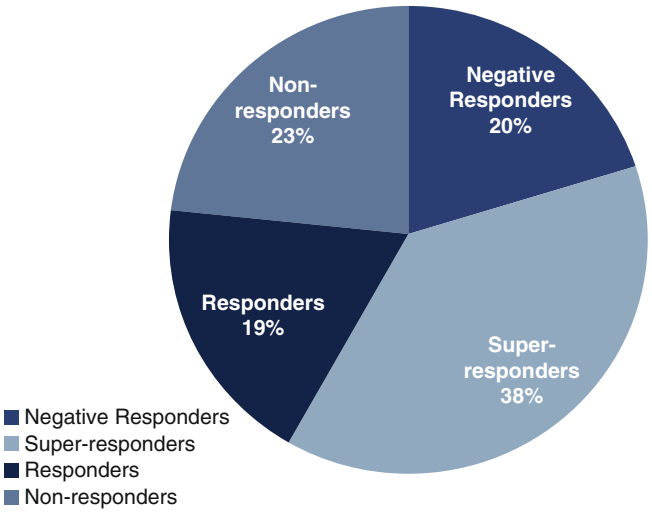

Fig. 1 Percentage of responders according to the extend of reduction in LVESV (Adapted of Oxford Textbook of Heart Failure 2011)

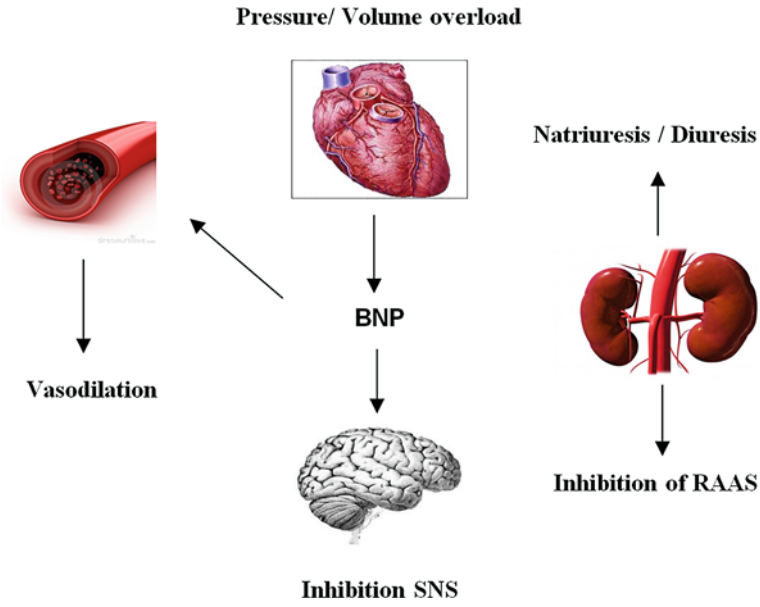

Fig. 2 Physiological effects of B- type natriuretic peptide (BNP). *RAAS* Renin–angiotensin–aldosterone system, *SNS* Sympathetic nervous system

Early and Sustained Effects of Cardiac Resynchronization Therapy on Biomarkers (BNP/NT- proBNP)

As indicated before, BNP and NT-proBNP are produced by ventricular cardiomyocytes in response to myocardial stretch and elevated ventricular filling pressures (Fig. 2). A higher baseline plasma concentration predicts a higher risk of all-cause mortality, sudden death, and death from heart failure. Elevated BNP at the time of CRT is prognostic of subsequent HF or death independently of the type of the device received. In some trials, CRT is associated with significant reductions in BNP levels during the follow-up time, whereas a similar pattern is not observed among patients who are not treated with the device Brenyon et al. 2013.

The CARE-HF trial demonstrates that CRT exerts a remarkable early and sustained reduction in plasma concentrations of NP levels when compared with pharmacological therapy alone in patients with moderate to severe chronic HF and ventricular dyssynchrony. These changes were most strongly associated to improvements in left ventricular function and reductions in mitral regurgitation. CRT has a more or less instantaneous effect on cardiac function and mitral valve regurgitation. The early reduction in NP shown in CARE-HF trial probably reflects the acute hemodynamic improvement that should reduce ventricular filling pressure and improve efficiency, and this would be expected to lead to beneficial ventricular remodeling (Berger et al. 2009).

The pattern of BNP change and the absolute BNP value at 1 year after CRT implantation is related to the echocardiographic response to the device and the risk of HF or death. Indeed, NT-proBNP may be the most robust, simple, objective prognostic marker in patients with HF. If the NPs are robust guides to prognosis, then it might be expected that change in NP might be a useful guide to the effectiveness of therapy Brenyon et al. 2013.

Plasma concentrations of NP might be used to guide changes in diuretic therapy, the need to increase doses of cardioprotective medication, and perhaps to guide when to implement CRT or implantable defibrillators. If natriuretic peptides are adopted as therapeutic target in patients with HF, then CRT appears to be a powerful additional intervention to achieve such a target in appropriately selected patients.

Conclusion

In an era in which the number of eligible candidates for CRT continues to increase, identifying optimal candidates for the therapy becomes especially important. In addition to device enhancements to individualize treatment and imaging modalities to detect ventricular dyssynchrony, monitoring BNP levels at baseline and during follow-up may be a powerful tool to further assess the response of patients with symptomatic HF treated with CRT.

Contribution of Inflammatory Mediators and Cardiac Extracellular Matrix Metabolism as Predictors of Response to Treatment by Cardiac Resynchronization Therapy

Heart failure (HF), the final common pathway for most cardiovascular conditions, incorporates a complex network of numerous molecular and cellular events that translates into profound alterations in structure and function of the cardiovascular system. The understanding of the complex pathophysiological mechanisms that underlie the syndrome of HF is constantly evolving, making the task of developing a single integrated theoretical model encompassing all aspects of this disease extremely challenging. Nevertheless, it is widely accepted that HF is triggered by an index event – an acute or chronic myocardial injury that impairs the pumping capacity of the heart. In order to counteract the impairment caused by the index event, autonomic, hormonal, immune, and inflammatory systems are activated with an initial protective role, trying to achieve a new level of homeostatic balance. However, continuous excessive activation of these initial compensatory mechanisms leads to detrimental consequences within the myocardium that are the base of progressive worsening HF and are referred collectively as cardiac remodeling (Gong et al. 2007). Therefore, cardiac remodeling can be defined as an adaptation of cellular and extracellular compartments of the heart to mechanical, hormonal, autonomic, and inflammatory stimuli that act in response to an index injury and lead

to detrimental modifications in structure and function of the heart (Rienks et al. 2014). In the pursuit of improving the prognosis of HF patients, current pharmacological and device therapies try to act on this deleterious remodeling process, aiming the reversion of the biological changes that constitutes the basis of the worsening cascade of HF.

A subset of patients with chronic HF present important abnormalities in ventricular conduction of electric stimuli that alter the timing and pattern of ventricular contraction, leading to suboptimal ventricular filling and contraction and prolonging the duration of mitral regurgitation. All these hemodynamic constraints impose an additional mechanical disadvantage to an already failing heart. CRT, through promotion of coordinated biventricular pacing, corrects this electromechanical dyssynchrony and eventually may induce a reverse cardiac remodeling, breaking the vicious cycle of heart failure progression. Much attention has been given to the molecular and cellular mechanisms that may underlie reverse cardiac remodeling induced by CRT. One of the most active lines of investigation focuses on the modulating effects of CRT on inflammatory mediators and cardiac extracellular metabolism. Besides shedding light into the complex network of HF pathogenesis, clarifying the molecular pathways underlying the reverse remodeling capability of CRT offers a huge translational opportunity to investigate potential predictors of CRT response in HF patients. In fact, in spite of its potential benefits, approximately 30 % of patients implanted with CRT devices do not show clinical improvement. CRT nonresponse remains a major clinical problem fueling an intense investigation in the pursuit of reliable predictors of CRT response in order to identify the so-called nonresponders before CRT implantation. Increasing the complexity of the subject, multiple definitions of CRT response have been proposed, namely a clinical response assessed by exercise capacity tests, quality-of-life questionnaires, and frequency of heart failure hospitalizations, heart transplantation, and cardiovascular death and an echocardiographic response assessed through change in left ventricular volumes, ejection fraction, or cardiac output (Brouwers et al. 2014).

The following section is on the role of inflammatory and extracellular matrix metabolism biomarkers in the assessment of response to cardiac resynchronizing therapy in heart failure patients and their potential application in improving patient selection to CRT.

Inflammatory Mediators

Persistent immune activation is a central feature in HF pathophysiology, comprehending a deregulated interplay of proinflammatory and inhibitory cytokines that exert toxic effects on both the heart and peripheral tissues. At the cellular and molecular level cytokines participate in the process of cardiac adverse remodeling by promoting myocyte hypertrophy, myocyte apoptosis, contractile dysfunction, and changes in the composition and structure of extracellular matrix Mann (2002). It has been shown that cytokines may be released from both the heart itself in response to end-diastolic wall stress and adrenergic activation and from peripheral tissues in

response to stagnant hypoxia and endotoxins released into circulation by translocated intestinal bacteria Rubaj et al. (2006).

The effect of CRT on inflammatory biomarkers has been inconclusive. Despite some contradictory reports published so far, probably a result of a marked heterogeneity in study design and a reduced number of patients, there seems to be emerging converging evidence in favor of a beneficial effect of CRT on inflammatory parameters. The most likely explanation for this is that corrected electromechanical dyssynchrony may have a potential to decrease local and peripheral production of inflammatory mediators McAlister et al. (2004). In fact, corrected electromechanical dyssynchrony may reduce the mechanical stress of the late-activated lateral wall of left ventricle leading to an improvement of global cardiac loading conditions and thus reducing the stimulus for local production of cytokines. On the other hand, improving electromechanical synchrony will improve cardiac output and consequently tissue perfusion reducing the inflammatory stimulus represented by local ischemia and possible intestinal bacterial translocation.

Selected studies regarding the prognostic role of inflammatory biomarkers on CRT outcome are resumed in Table 1. A multitude of inflammatory mediators have been studied, but most evidence regards high-sensitivity C Reactive Protein (hsCRP) and Tumor Necrosis Factor α (TNFα).

High-sensitivity C Reactive Protein: hsCRP is synthesized and secreted by hepatocytes in response to proinflammatory cytokines and contributes to HF progression by upregulating the production of macrophage proinflammatory cytokines (IL-6, TNF-α, and IL1β), oxygen species formation, and expression of enzymes responsible for extracellular matrix turnover. In terms of HF prognosis, hsCRP has solid evidence pointing to association of high levels with increased mortality Rubaj et al. (2013).

Regarding the prognostic impact of hsCRP levels on CRT response, evidence has been conflicting. Brouwers et al., Theodarakis et al., and Glick et al. did not find significant differences in either baseline or after CRT implantation hsCRP levels between CRT responders and nonresponders Glick et al. (2006); Theodorakis et al. (2006); Brouwers et al. (2004). However, Cai et al., Rujab et al., and Kamioka et al. found that CRT responders had lower baseline and a greater decrease in hsCRP levels than nonresponders Rubaj et al. (2006); Kamioka et al. (2012); Cai et al. (2014) .

Tumor Necrosis Factor α: TNFα has been implicated in several aspects of HF pathogenesis by exerting a negative inotropic effect, triggering apoptosis in cardiomyocytes, and activating enzymes that degrade extracellular matrix Rordorf et al. (2014). In combination with IL6, TNFα and its soluble receptors are stronger predictors of HF mortality than traditional factors such as NYHA class, left ventricular ejection fraction, and maximal oxygen consumption Rauchhaus et al. (2000). Recently has emerged the concept that TNFα may be able to provide information on the degree of remodeling in patients with HF, with higher levels being associated to more advanced and possibly irreversible remodeling Rordorf et al. (2014). Similar to hsCRP, evidence regarding the prognostic impact of TNFα levels on CRT response is not consensual. On the one hand, Rordorf et al. (2014). found that the rate of

Table 1 Selected studies concerning inflammatory mediators and their prediction of cardiac resynchronization therapy response

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
(Stanciu et al. 2013)	Prospective study Repeated measures design (before and after CRT implantation)	27	IL-1β, IL-6 and IL-8	12 months	CRT responder defined as more than 10 % reduction in left ventricle end systolic volume and improvement in NYHA functional class in at least one class and no heart transplantation or death caused by cardiovascular causes	Circulating levels of IL-1β, IL-6 and IL-8 decreased from their baseline values
(Boriani et al. 2006)	Prospective study Repeated measures design (before and after CRT implantation)	32	IL-6, TNF and soluble TNF receptors 1 and 2 (sTNFR1 and sTNFR2)	3 months	CRT responder defined as ≥1 NYHA class reduction or ≥15 % reduction in left ventricle end systolic volume	Serum levels of IL-6, TNF and sTNFR1 and sTNFR2 did not change from baseline to follow up Baseline levels of IL-6, TNF and sTNFR1 did not differ between CRT responders and non responders
(Brouwers et al. 2014)	Prospective study Repeated measures design (before and after CRT implantation)	105	CRP, IL-6, TNFα, sTNFR1 and sTNFR2	14 months	Objective CRT response defined as a reduction of ≥15 % in left ventricular end systolic volume and Subjective CRT response defined as an improvement of ≥10 points in patient-reported health status assessed with the Kansas City Cardiomyopathy Questionnaire	Baseline concentrations of inflammatory markers did not differ between the objective CRT responders and non responders. Both objective CRT responders and non responders showed a significant decrease in TNFα levels from baseline to 14 months follow up. The other inflammatory markers did not change significantly over time in both groups The subjective CRT responders had significantly lower baseline levels of TnFα compared to non responders. Subjective responders showed a significant decrease in BNP, TNFα and sTNFR1 levels from baseline to 14 months follow

						up. Subjective non responders had a decrease in TNFα over time and an increase in IL-6, sTNFR1 and sTNFR2 levels
(Cai et al. 2014)	Prospective study Repeated measures design (before and after CRT implantation)	232	High sensitivity C-reactive protein (hsCRP)	6 months	CRT responders defined as ≥1 NYHA class reduction combined with an absolute increase ≥5 % in LVEF during 6 month follow up	Baseline hsCRP values as well as 6-month hsCRP levels were significantly lower in patients who responded to CRT than in those who did not Patients with low 6 month hsCRP values displayed the largest reduction in LVEDD and increases in LVEF
(Glick et al. 2006)	Prospective study Repeated measures design (before and after CRT implantation)	32	hsCRP	2 weeks	CRT responder defined as ≥1 NYHA class reduction after 1 month	Levels of hsCRP decreased significantly 2 weeks after implantation. Baseline levels of hsCRP or their drop after 2 weeks of CRT implantation did not correlate with clinical outcome
(Kamioka et al. 2012)	Prospective study Repeated measures design (before and after CRT implantation)	65	hsCRP	6 months	CRT responder defined as >15 % reduction in LVESV	Baseline hsCRP was significantly higher in patients who did not respond to CRT than in those who did HsCRP was the strongest predictive factor for cardiac death
(Lappegard and Bjornstad 2006)	Prospective study Repeated measures design (before and after CRT implantation)	8	Monocyte chemoattractant protein 1 (MCP-1), interleukin-8 (IL-8), interleukin 6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor α (TNFα), interleukin 10 (IL-10) and complement activation products	6 months	Not defined	There was a significant reduction in plasma levels of MCP-1, IL-8 and IL-6. No changes were observed in the levels of IL1β, TNFα, IL-10 and complement activation products
(Michelucci et al. 2007)	Prospective study Repeated measures design (before and after CRT implantation)	140	IL-6, hsCRP	6 months	Not defined	In patients who survived free from clinical events, IL-6 and hsCRP levels significantly decreased from baseline to 6 months follow up. In patients who has an

(*continued*)

Table 1 (continued)

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
						adverse clinical event, no significant changes were observed in both IL-6 and hsPCR from baseline to 6 months follow up
(Przybyla et al. 2011)	Prospective study Repeated measures design (before and after CRT implantation)	38	IL-6, interleukin 18 (IL-18), CRP	3 months	Not defined	The level of IL-6 decreased from baseline to 3 months follow up. No change in CRP and IL-18 levels were observed
(Rordorf et al. 2014)	Prospective study Repeated measures design (before and after CRT implantation)	91	TNFα and IL-6	6 months	CRT response defined as a decrease ≥15 % in left ventricular end systolic volume at 6 months	Baseline circulating IL-6 was not correlate with reverse remodeling. Baseline circulating IL-6 did not predict response to CRT Baseline TNFα was significantly predictive of left ventricular end systolic volume reduction. The rate of response to CRT was significantly different according to baseline circulating TNFα: there was a linearly decreasing proportion of patients with LVESV reduction ≥15 % from the lower through the intermediate to the upper tertile of TNFα level Patients with the higher baseline circulating TNFα had the worst clinical outcome (composite endpoint of cardiac death, heart failure hospitalization and urgent cardiac transplantation)

(Rubaj et al. 2006)	Prospective study Repeated measures design (Rignt ventricular pacing to biventricular pacing)	28	CRP, TNFα and IL-6	48 h	CRT responder defined as an increase >10 % in cardiac output	TNFα and IL6 measured during RV pacing (baseline) did not differ between the responders and the non responders Levels of TNFα and IL-6 significantly decreased following the change in pacing mode from right ventricular pacing to biventricular pacing Levels of CRP did not change following the change in pacing mode
(Rubaj et al. 2013)	Prospective study Repeated measures design (Biventricular pacing followed by Rignt ventricular pacing followed again by biventricular pacing)	54	High sensitivity CRP, IL-6	48 h after CRT-off	CRT responder defined as improvement of at least 1 NYHA class and absolute increase in LVEF >10 %	A significant increase in serum concentrations of hsCRp and IL-6 was observed in CRT responders after CRT interruption. When CRT was switched on again, a significant reduction in IL-6 and cRP was observed in this subgroup of patients. In CRT non responders, switching biventricular pacing to right ventricular pacing did not lead to significant changes in hsCRP and IL-6
(Shinohara et al. 2011)	Prospective study Repeated measures design (before and after CRT implantation)	27	Hs-CRP	6 months	CRT responder defined as ≥15 % absolute decrease in left ventricular end systolic volume	In responders, serum levels of hs-CRP significantly decrease after 6 months follow up. Non responders did not show any change in hs-CRP levels after 6 months follow up
(Tarquini et al. 2009)	Prospective study Repeated measures design (before and after CRT implantation)	47	TNFα, TNF soluble receptors sTNFR1 and sTNFR2	12 months	CRT responder defined as ≥15 % absolute decrease in left ventricular end systolic volume	Baseline levels of TNFα and sTNFR1 and sTNFR2 were not significantly different in responders and non-responders No significant changes in levels of TNFα and sTNFR1 and sTNFR2 were observed after 12 months of CRT

(*continued*)

Table 1 (continued)

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
(Theodorakis et al. 2006)	Prospective study Repeated measures design (3 months of no pacing followed by 3 months of biventricular pacing followed by 3 months of no pacing again)	20	CRP, TNFα, sTNFR1 and sTNFR2, adhesion molecules sICAM-1 and sVCAM-1	3 months + 3 months	Not defined	TNFα and its receptors showed a decrease after 3 months of pacing and a further decrease after the ensuing 3 months of no pacing. IL-6 and sICAM-1 levels decreased after 3 months of biventricular pacing and remained lower during the 3 months off pacing. No changes were observed in the levels of CRP and sVCAM-1
(Marin et al. 2011)	Prospective study No control group	36	CRP	4 months	Not defined	Following CRT, CRP levels remained unchanged

response to CRT was significantly different according to baseline TNFα – from the lower to the upper tertile of TNF-α, left ventricular volumes were progressively reduced after CRT Rordorf et al. (2014). On the other hand, Tarquini et al. showed that baseline levels of TNFα were not significantly different in CRT responders and nonresponders Tarquini et al. (2009).

Cardiac Extracellular Matrix Metabolism

The cardiac extracellular matrix is a metabolic active network consisting of proteins in which cardiac cells reside. Besides its plastic role, conferring support to efficient contraction and relaxation of cardiomyocytes, the cardiac matrix plays an important role in mediating cellular crosstalk and metabolic exchange (Li et al. (2014)).

Adverse cardiac remodeling during the course of HF is accompanied by changes in the structure and composition of extracellular matrix. It has been proposed that during early stages of HF inflammation favors collagen degradation that contributes to ventricular dilatation. As heart failure evolves, inflammation becomes chronic and different molecular pathways are activated with the resultant event being excessive collagen deposition instead of collagen degradation Mann (2002). The result of this metabolic shift is the development of undue myocardial stiffness that impairs both filling and pumping functions and provides a structural subtract to arrhythmogenicity.

Debate still exists regarding the potential effects of CRT on extracellular matrix metabolism. Nevertheless, most evidence points to a beneficial effect of CRT, which counteracts the persistent fibrogenesis of advanced HF and hence promotes reverse remodeling. Recently, some extracellular matrix biomarkers have emerged as useful tools in the prediction of CRT response as it is believed that subsets of HF patients in different metabolic stages of extracellular matrix remodeling may derive disproportionate benefit from this therapy. Most evidence regarding this subject concerns enzymes involved in collagen metabolism and galectin-3.

Collagen: Collagen type I and collagen type III are the main proteins of cardiac extracellular matrix. While collagen type I with its thicker fibers provides tensile strength to extracellular matrix, collagen type III being thinner yields elasticity. Both types of collagen are synthesized by fibroblasts from the assembly of three procollagen- α- chains. During collagen synthesis, amino and carboxy propetides of procollagen I and III (PINP, PICP, PIIINP, PIIICP) are cleaved and released into circulation. Collagen fibers are degraded by enzymes called metalloproteinases (MMPs) that can be inhibited by specific tissue inhibitors of metalloproteinases (TIMPs). As a result of MMP action during collagen degradation, small peptides may be released into the circulation as it is the case of the carboxyterminal telopeptide of type I collagen (ICTP). Collagen metabolism can be easily assessed noninvasively by measuring the ratio of MMP to TIMP activity or the levels of collagen's circulating by-products – PINP, PICP, PIIINP, and PIIICP to evaluate collagen type I and type III synthesis, respectively, and ICTP to evaluate collagen type I degradation. Regarding the prognostic impact of collagen metabolism on CRT

Table 2 Selected studies concerning cardiac extracellular matrix metabolism biomarkers and their prediction of cardiac resynchronization therapy response

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
(Dong et al. 2011)	Prospective study Repeated measures design (before and after CRT implantation)	45	Amino-terminal propeptide of type III procollagen (PIIINP)	3 and 6 months	CRT responder defined as 15 % or greater reduction in left ventricular end-systolic volume index	The baseline PIIINP was lower in CRT responders than non responders PIIINP remained unchanged after 6 months of CRT
(Francia et al. 2011)	Prospective study Repeated measures design (before and after CRT implantation)	18	Osteopontin (OPN) –TGFβ1 axis	8,5 + - 4 months	CRT responder defined as 10 % or greater reduction in left ventricular end systolic volume	CRT responders showed a non significant trend towards higher baseline plasma OPN and TGFβ1 as compared to non responders Compared to baseline, circulating levels of OPN were significantly reduced in CRT responders and increased in non responders. TGFβ1 showed a trend towards reduction in responders while unchanged in non-responders

(Garcia-Bolao et al. 2006)	Prospective study Repeated measures design (before and after CRT implantation)	38	Carboxy-terminal propeptide of type I procollagen (PICP)	12 months	CRT responder defined as increase in the distance walked in 6 min by more than 10 % and no heart transplantation or death caused by heart failure	Baseline PICP was higher in responders than non responders At 1 year PICP decreased in responders and increased in non responders
(Hessel et al. 2007)	Prospective study Repeated measures design (before and after CRT implantation)	64	Tenascin-C (TNC), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9)	6 months	CRT responder defined as 10 % or greater reduction in left ventricular end systolic volume	At baseline no significant differences in TNC, MMP-2 and MMP-9 were observed between responders and non-responders At 6 months follow up, TNC and MMP-9 showed a significant reduction in responders while remained unchanged in non-responders MMP-2 levels remained unchanged in both responders and non-responders

(*continued*)

Table 2 (continued)

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
(Li et al. 2013)	Prospective study Repeated measures design (before and after CRT implantation)	27	MMP-9, tissue inhibitor of MMP-9 (TIMP-1), carboxyterminal propeptide of type I procollagen (PICP) and carboxyterminal telopeptide of type I collagen (ICTP)	3 months	Not defined	At 3 months follow up, the CRT group showed a significant reduction in MMP-9, TIMP-1, ICTP and MMP9/TIMP-1 and a significant increase in the PICP/ICTP ratio levels compared with pretreatment values At 3 months follow up, there was a negative correlation between left ventricle end diastolic diameter indexed to body surface area and the PICP/ICTP ratio in the CRT group

(Lopez-Andres et al. 2012)	Prospective study based on a previous randomized controlled trial (CRT vs no CRT)	260	Galectin-3 (Gal-3), PIIINP, amino-terminal popeptide of type I procollagen (PINP), ICTP and matrix metalloproteinase-1 (MMP-1)	18 months	Treatment efficacy assessed according to three criteria from the CARE-HF trial: survival without unplanned hospitalization for worsening heart failure; survival and left ventricle ejection fraction >35 %; survival and NT-proBNP levels <1000 pg/mL	There was no difference in median baseline levels of extracellular cardiac matrix biomarkers between control and CRT groups and mean values varied little throughout the 18 month follow up in both treatment groups Extracelullar cardiac matrix biomarkers at baseline did not predict the response to CRT MMP-1 concentration was associated with the outcome of death or LVEF $\leq$ 35 % at 18 months
(Marin et al. 2011)	Prospective study Repeated measures design (before and after CRT implantation)	36	MMP-1, MMP-2, TIMP-1 and CITP	4 months	Not defined	Following CRT, MMP-1 and MMP-2 levels were significantly increased at 4 months TIMP-1 and CITP remained unchanged

(*continued*)

Table 2 (continued)

Author (year)	Study design	Number of patients	Biological markers	Follow-up (months)	Assessment of CRT response	Main results
(Stanciu et al. 2013)	Prospective study Repeated measures design (before and after CRT implantation)	27	MMP-2 and tissue inhibitor of matrix metalloproteinase-2 (TIMP-2)	12 months	CRT responder defined as more than 10 % reduction in left ventricle end systolic volume and improvement in NYHA functional class in at least one class and no heart transplantation or death caused by cardiovascular causes	Serum levels of MMP-2 and MMP-2/TIMP-2 ratio decreased from baseline during follow up LVEF correlated negatively with MMP-2/ TIMP-2 ratio at follow –up
(Stolen et al. 2014)	Prospective study based on a previous randomized controlled trial (CRT-D vs ICD-only)	654	Gal-3	12 months	Composite primary endpoint from MADIT-CRT: nonfatal heart failure event or death from any cause whichever occurred first	Patients with Gal-3 values in the highest quartile derived a disproportionately larger benefit from CRT-D in comparison with patients with ICD-only. The absolute reduction in primary event rate attributable to CRT-D relative to ICD-only in the high gal-3 group was 11,2 fewer primary events per 100 patients-year and in the low gal-3 group it was 2,1 fewer primary events per 100 patient-years

(Umar et al. 2008)	Prospective study Repeated measures design (before and after CRT implantation)	64	PINP, PIIINP, ICTP, TIMP-1 and pro MMP1	6 months	CRT responder defined as more than 10 % reduction in left ventricle end systolic volume	Responders demonstrated an increase in serum PINP and PIIINP during follow up. In non responders, serum PINP and PIIINP remained unchanged during follow up At baseline responders had significantly lower serum PINP than non responders Serum levels of ICTP, proMMP1, TIMP-1 and proMMP1/TIMP1 did not differ between baseline and follow-up nor did they differ between responders and non-responders
(Vondrakova et al. 2012)	Prospective study Repeated measures design (before and after CRT implantation)	18	Gal-3	2 months	Not defined	Serum levels of Gal-3 decreased from baseline to follow-up

response, evidence has been conflicting. Garcia-Bolao et al. found that baseline PICP was higher in responders than in nonresponders. On the other hand Umar et al. showed that responders had lower baseline PINP than nonresponders. Other inconsistencies concerning MMP/TIMP ratios and MMP levels have been reported.

Galectin-3: Galectin-3 (Gal-3) is a protein secreted by activated macrophages that plays an important role in promoting fibrosis through fibroblast proliferation and collagen synthesis. A prospective study derived from a randomized control trial has shown that patients with gal-3 levels in the highest quartile derived a disproportionately larger benefit from CRT-D in comparison with patients with ICD only.

Conclusion

CRT has assumed a central role in the treatment of HF patients with evidence of electromechanical dyssynchrony. However, at least 30 % of patients with implanted CRT devices do not show the expected clinical improvement. As we advance in the understanding of the cellular and molecular mechanisms that underlie the reverse remodeling promoted by CRT, novel biomarkers with the ability to accurately predict response versus nonresponse to CRT are expected to arise. Such a breakthrough with the consequent improvement in the selection of patients to CRT would entail a huge clinical and economic impact. In the pursuit of this objective, larger prospective studies with adequate design and longer follow-up times are needed.

Potential Applications of Circulating Endothelial Progenitor Cells in CRT

Currently, cardiac resynchronization therapy (CRT) using biventricular pacing is a standard of care in the management of advanced heart failure (HF) Brignole et al. (2013). However, based on current selection criteria, a considerable proportion of eligible patients still fail to benefit from this treatment Daubert et al. (2012). Identifying reliable predictors of effectiveness of CRT remains a major challenge in clinical practice, particularly from the perspective of patient selection.

Endothelial dysfunction is an important underlying mechanism in the pathophysiology of HF, which has recently been suggested as an independent predictor of CRT response Akar et al. (2008). Endothelial progenitor cells (EPCs) harbor a recognized capacity to proliferate and differentiate into mature endothelial cells, contributing in vivo to both reendothelialization and neoangiogenesis, and therefore to the maintenance of endothelial integrity Liao et al. (2010). Furthermore, it has been recently suggested that patients with higher circulating EPC levels have a greater neovascularization potential and are more likely to exhibit a positive response to CRT António et al. (2014).

Cardiac Remodeling in HF Patients and Reverse Remodeling After CRT

A common aspect of HF, irrespective of the underlying etiology, is the development of cardiac remodeling, which describes the changes in LV mass, volume, shape, and composition of the ventricle in response to the mechanical (stress and strain) and systemic neurohormonal activation. The alterations that occur in the failing myocardium may be divided into those that occur in the cardiac myocytes as well as those which occur in the extracellular matrix (Table 3). Ultimately, these changes lead to progressive LV dilation, increased sphericity of the ventricle, and progressive decline in contractile function Mann et al. (2012) and Li et al. (2014).

From several large clinical trials it is becoming increasingly clear that CRT leads to decreased left ventricular (LV) volume and mass, and restores a more normal elliptical shape of the ventricle. These salutary changes have been called "reverse remodeling" Linde et al. (2002), Abraham et al. (2002), Cleland et al. (2005), Moss et al. (2009). Remarkably, there are subsets of patients who undergo a reverse remodeling and whose clinical course is free of future heart failure events – myocardial recovery. However, exactly what causes this cardiac reverse remodeling resulting from CRT and what subcellular mechanisms are involved are only poorly understood. It is even less clear why a significant number of patients do not respond positively to CRT and why some patients exhibit molecular reverse remodeling but this does not translate to clinical recovery.

Endothelial Progenitor Cells as a Predictor of CRT Response

A growing body of evidence strongly demonstrates that endothelial dysfunction plays an important role in the pathogenesis and progression of HF. Moreover,

Table 3 Cellular, molecular and anatomic changes that occur during cardiac remodelling in HF patients

Myocyte defects	Myocardial defects		Reversal of abnormal LV geometry
Hypertrophy	Myocyte death	Apoptosis	LV dilation
Fetal gene expression		Necrosis	LV wall thinning
β-adrenergic desensitization		Autophagy	Mitral valve incompetence
Myocytolysis	Alterations in extracellular matrix	Matrix degradation	
Excitation contraction coupling		Replacement fibrosis	
Cytoskeletal proteins		Angiogenesis	
Myocyte energetics			

endothelial dysfunction seems to be correlated with disease severity and prognosis in HF patients. Of note, it has been recently demonstrated that endothelial function independently predicts CRT response Akar et al. (2008).

Endothelial progenitor cells are endothelial and hematopoietic progenitor cells having a recognized capacity to proliferate and differentiate into mature endothelial cells, contributing to the process of vasculogenesis, repairing the damaged and dysfunctional endothelium. As circulating EPC numbers seem to be related to endothelial function, EPCs have been proposed by Liao YF et al. as a surrogate biological marker of endothelial function Liao et al. (2010).

It has been demonstrated that circulating EPCs correlate with favorable left ventricular remodeling after myocardial infarction. Therefore, it is conceivable that circulating EPC levels also contribute for the reverse remodeling associated with CRT and influence the response to this therapy. Remarkably, we have published data showing a positive correlation between baseline EPC levels and LVESV reduction after CRT suggesting a role of EPCs in the reverse remodeling observed with resynchronization (Fig. 3). Additionally, in our work responders to CRT showed significantly higher levels of EPCs by comparison with nonresponders, reinforcing the hypothesis that EPCs may have an important role in reverse remodeling and CRT response António et al. (2014).

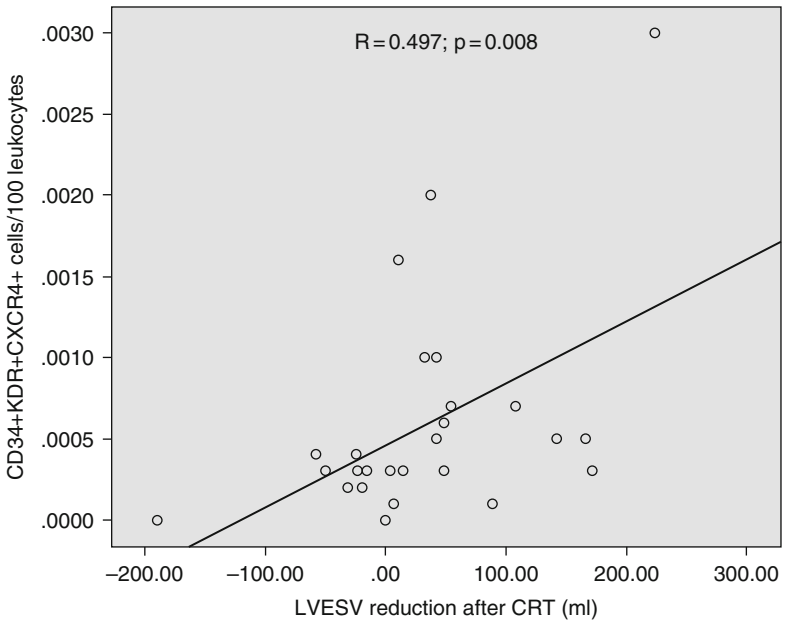

Fig. 3 Comparison of baseline EPCs levels between responders and non-responders to CRT (Adapted from Antonio N et al. Pacing Clin Electrophysiol. 2014)

Conclusions

Despite the high effectiveness of CRT in severe chronic HF, the rate of nonresponders remains an important problem. In fact, up to 30 % of patients treated with CRT do not exhibit the desirable reverse remodeling and cardiac recovery. Circulating EPCs, a surrogate marker of endothelial function, may help identifying the subset of HF patients with greater neovascularization potential and higher probability to undergo reverse remodeling and benefit from CRT. Therefore, the quantification of circulating EPC levels may be an important additional tool to identify the best CRT candidates.

Renal Function and Cardiac Resynchronization Therapy

Cardiac and renal functions have a well-known interdependent relationship as there are a number of important bidirectional interactions between heart and kidney diseases. Chronic kidney disease (CKD) is present in more than half of patients with heart failure (HF) and approximately two-thirds of patients hospitalized with HF have renal insufficiency (Smith et al. 2006; McAlister et al. 2004a). In both the acute setting and long-term phase of HF, even small decreases in glomerular filtration rate (GFR) are associated with an adverse prognostic impact (de Silva et al. 2006; Coca et al. 2007). CRT significantly improves outcomes in a group of patients with advanced HF and renal function can be considered to improve the selection of patients, having important prognostic implications.

The serum creatinine level is usually used as a surrogate to estimate GFR, as kidney function is related directly to the urine creatinine excretion and inversely to the serum creatinine. As serum creatinine is also affected by factors unrelated to renal function, such as age, sex, race, and lean muscle mass, two formulas are used widely to estimate kidney function from serum creatinine: Cockcroft-Gault and four-variable Modification of Diet in Renal Disease (MDRD).

While CRT represents one of the most important advances for the treatment of advanced HF, nonresponse in a large number of patients continues to be problematic. The renal function biomarkers have been studied in order to improve patient selection to CRT. In a subgroup analysis of CARE-HF trial, the benefit of CRT-P on global mortality and cardiovascular hospitalization was preserved in patients with GFR less than 60.3 mL/min/1.73 m^2 (Cleland et al. 2006). In the REVERSE trial, there was no evidence of differential reduction in the primary endpoint of clinical response considering the GFR, but patients with a GFR < 60 were observed to have less left ventricular structural remodeling (Linde et al. 2008; Mathew et al. 2012) . In an observational analysis of Adelstein et al. comparing outcomes of CRT-D patients with a cohort of similar patients who received an ICD only, patients with moderate CKD (GFR 30–59 mL/min/1.73 m^2) had a significant survival advantage with CRT, associated with improved renal and cardiac function (Adelstein et al. 2010). On the other hand, patients with baseline severe CKD (GFR <30 mL/min/1.73 m^2) had a

poor survival despite CRT-D, which appeared to confer little echocardiographic benefit despite modest improvement in renal function.

Although serum creatinine–based estimating equations to GFR have been the most studied, the role of other renal biomarkers on CRT management was already studied. The effect of the ratio of blood urea nitrogen (BUN) to creatinine on response to CRT therapy was considered in a post hoc subgroup analysis of the MADIT-CRT trial (Goldenberg et al. 2010). The patients were dichotomized into two groups using the BUN/creatinine ratio value of 18 and it was found that the reduction of HF hospitalization or death was greater in patients with higher ratio. The authors concluded that prerenal azotemia, reflected in high BUN/creatinine ratio, is a marker for decreased circulation blood volume and identifies patients at higher risk for HF and, hence, a group with better response to CRT.

Cystatin C is a cysteine protease inhibitor that is produced at a relatively constant rate from all nucleated cells, and serum cystatin C has been proposed to be a more sensitive marker of early GFR decline than plasma creatinine. A prospective study from Yamamoto et al. showed that serum cystatin C level prior to CRT device implantation independently predicts mortality and morbidity (Yamamoto et al. 2013). The association of cystatin C with mortality is even superior to that of serum BNP level, providing an accurate risk stratification of CRT patients.

In summary, despite the higher mortality associated in CKD patients, the benefit of CRT on clinical outcomes seems to be preserved. Renal biomarkers have been studied in this context and could identify subgroups of patients with better response rates to CRT.

Summary Points

- Despite the high effectiveness of CRT in chronic HF, a significant proportion of patients selected using conventional criteria do not appear to benefit from CRT.
- Identifying reliable predictors of effectiveness of CRT remains a major challenge in clinical practice.
- In order to reduce the percentage of nonresponders to CRT, it could be helpful to use new promising tools, such as inflammatory biomarkers, BNP, and endothelial progenitor cells, in a multimodal approach to improve patient selection.
- Monitoring BNP levels at baseline and during follow-up may be a powerful tool to further assess the response of patients with symptomatic HF treated with CRT.
- Circulating EPCs, a surrogate marker of endothelial function, may help identifying the subset of HF patients with greater neovascularization potential and higher probability to undergo reverse remodeling and respond to CRT.
- As we advance in the understanding of the cellular and molecular mechanisms that underlie the reverse remodeling promoted by CRT, novel biomarkers with the ability to accurately predict response versus nonresponse to CRT are expected to arise.

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