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Effects of cardiac resynchronization therapy on systemic inflammation and neurohormonal pathways in heart failure

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Abstract

Background: *The effect of cardiac resynchronization therapy (CRT) on systemic inflammation and neurohormonal alterations associated with heart failure is not well characterized. Accordingly, we aimed to assess the long term effects of CRT on systemic inflammation and neurohormonal factors in heart failure patients.*

Methods and results: *In 47 HF patients (NYHA III–IV) we evaluated, at baseline and after one year of CRT: TNF-α, TNF soluble receptors (sTNFR1 and sTNFR2), insulin-like growth factor-1α (IGF-1α), adiponectin, norepinephrine, pro-atrial natriuretic peptide (pro-ANP), N-terminal-pro-brain natriuretic peptide (NT-proBNP) and angiotensin II, NYHA functional class, quality of life (the Minnesota Living with Heart Failure questionnaire), a 6-minute walk test and an echocardiogram. Long-term CRT decreased activation of renin–angiotensin system (RAS) only in patients with reverse remodelling. It failed to prevent a decline in adiponectin levels, regardless of reverse remodelling. NT-proBNP remained unchanged in patients with reverse remodelling, whereas its levels increased in those without reverse remodelling. IGF-1α increased with CRT, whereas CRT had no effect on pro-ANP and inflammatory markers.*

Conclusions: *Long-term CRT is associated with decreased RAS activation and stabilization of NT-proBNP in heart failure patients with reverse remodelling. Long-term CRT, with or without reverse remodelling, does not affect systemic inflammation and fails to prevent a decline in adiponectin.* (Cardiol J 2009; 16, 6: 545–552)

Key words: resynchronization therapy, heart failure, neuro-hormonal pattern

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for those patients with New York Heart Association (NYHA) class III/IV chronic systolic heart failure (CHF) and left ventricular (LV) dyssynchrony, as evidenced by a prolonged QRS duration beyond 120 ms [1].

By restoring co-ordinated contraction, CRT promotes LV reverse remodelling and improves symptoms, exercise capacity and quality of life in patients with CHF [1]. Several animal studies and clinical pilot trials have suggested that down-regulation of inflammatory cytokines may improve cardiac performance [2]. The effect of CRT on systemic inflammation and neurohormonal alterations associated with CHF is not well understood [2–6].

Accordingly, the present study aims to assess the long-term (12 months) effects of CRT on the systemic inflammation and neurohormonal factors in CHF patients with NYHA III–IV functional class. In addition, we evaluated whether 1-year CRT influence on the neurohormonal pattern was different in patients who developed reverse remodelling (responders) from those who did not (non-responders).

Methods

Study population and protocol

In this prospective randomized study, we enrolled 60 CHF patients referred to our institute from January 2007 to December 2008 for biventricular pacemaker implantation. Patients had an advanced CHF (NYHA III–IV functional class) due to dilated cardiomyopathy of any etiology, with a left ventricular ejection fraction (LVEF) < 35% [7] and QRS duration ≥ 120 ms. All patients had been receiving optimal medical therapy for at least three months prior to enrolment.

Exclusion criteria were: previous pacemaker implantation, significant valvular disease requiring surgical correction, acute myocarditis, acute coronary syndrome within three months of enrolment, and severe chronic obstructive pulmonary disease. Patients had no clinical evidence of inflammatory, neoplastic, or metabolic diseases as assessed by clinical history, examination and laboratory tests.

The study was approved by the Institutional Review Board and Local Ethical Committee. Informed consent was obtained from each patient.

Eight patients refused to participate in the study and five were lost to follow-up. Thus, 47 CHF patients who received biventricular pacemaker implantation were studied.

Assessment of NYHA functional class, quality of life (QoL) using the Minnesota Living with Heart Failure questionnaire, a 6-minute walk test (WT) and an echocardiogram were performed at baseline (before pacemaker implantation) and after 12 months of CRT therapy.

Measurement of systemic inflammation and neurohormonal alterations

After a 30-minute bed rest, blood samples were collected to measure serum TNF-α, TNF soluble receptors (sTNFR1α and sTNFR2), insulin-like growth factor-1α (IGF-1α), adiponectin, norepinephrine, pro-atrial natriuretic peptide (pro-ANP), N-terminal-pro-brain natriuretic peptide (NT-proBNP) and angiotensin II. Blood samples were collected before biventricular implantation and after 12 months of CRT.

To measure TNF-α, sTNFR1, sTNFR2, IGF-1α, adiponectin, norepinephrine, and angiotensin II, 10 mL of venous blood was collected in a sterile tube containing EDTA at 4°C, and rapidly separated after centrifugation. For pro-ANP and NT-proBNP measurement, 7 mL of venous blood was collected in an ice-chilled tube containing EDTA and aprotinin (Trasylol, Bayer; 550 kallicrein inhibiting units). All samples were centrifuged at 1,700 g for 20 min at 4°C and stored at –20°C until analyzed. All measurements were performed in duplicates.

Solid phase enzyme amplified sensitivity immunoassay was used to measure plasma levels of IGF-1α, TNFα, sTNFR1 and sTNFR2 (BIOSOURCE Europe S.A., Nuvelles, Belgium). Plasma levels of adiponectin were measured using the Mediagnost kit ELISA (Reutlingen, Germany). Plasma levels of NT-proBNP and pro-ANP were measured using a competitive enzyme immunoassay (Biomedica Gruppe, Vienna, Austria). Plasma levels of norepinephrine were measured using ^{125}I norepinephrine/epinephrine RIA (DRG Instruments GmbH, Germany). Plasma levels of angiotensin II were measured using TEMA Ricerca srl (Bologna, Italy).

Creatinine serum levels were measured in all participants, as an estimate of renal function.

Echocardiography

Standard echocardiography including Doppler was performed using a commercially available system (Vivid 7; General Electric-Vingmed, Milwaukee, Wisconsin, USA). Left ventricular end-diastolic (LVEDV), end-systolic (LVESV) volumes and

Table 1. Demographic characteristics of the study participants.

	All participants (n = 47)	Non-responders (n = 20)	Responders (n = 27)	P
Age (years)	71.02 ± 9.16	69.30 ± 9.68	72.30 ± 8.72	NS
Body mass index [kg/m^2]	25.85 ± 3.31	25.79 ± 2.96	25.90 ± 3.60	NS
Males/females	27/20	11/9	16/11	NS
CrCl [mL/min/1.73 m^2]	49.29 ± 15.42	52.41 ± 14.74	46.98 ± 15.77	NS
Etiology (%)				
Non ischemic	53.19	60	48	NS
ACE-inhibitors (%)	100	100	100	NS
Beta-blockers (%)	68	60	74	NS
Diuretics (%)	97	97	97	NS
Spironolactone (%)	53	55	52	NS
ICD (%)	42	33	48	NS

ICD — implantable cardioverter-defibrillator; ACE — angiotensin-converting enzyme

LVEF were calculated using the biplane Simpson's rule as an average of at least three measurements and then indexed to body surface area, and reported as LVEDVi (indexed LVEDV) and LVESVi (indexed LVESV) [8]. Patients were defined as responders if their LVESV was reduced at follow-up by at least ≥ 15% compared with baseline indicating reverse remodelling [6, 7]. Patients were defined as non-responders if their LVESV at follow-up remained unchanged or was reduced by < 15% compared with baseline.

Diastolic filling time was defined as the time between the onset of the E wave and the end of the A wave by pulsed wave Doppler placed at the mitral valve tips in the apical 4-chamber view.

Pacemaker implantation

After enrolment and baseline assessments, biventricular devices were implanted as previously described [6, 9]. Briefly, the LV pacing lead was inserted transvenously via the subclavian vein with the help of a guiding catheter into the coronary sinus, and then positioned in the lateral or posterolateral cardiac vein when possible. LV lead was inserted in the lateral or posterolateral vein in 39 patients (81%), while in the remaining patients it was inserted in the anterior vein. The atrioventricular delay was echocardiographically optimized to obtain the longest filling time or the best myocardial performance index one week after implantation [10, 11].

All patients included in the study underwent CRT alone or in combination with an implantable cardioverter-defibrillator over a 12 month period.

Data analysis

Statistical analysis was performed using a software program (SPSS for Windows, SPSS Inc., Chicago, Illinois, USA, version 13.0). All values were log-transformed due to their non-normal distribution. In addition, data are presented as mean ± SD. Baseline categorical data were compared by means of the Fisher exact test. To compare continuous variables, the Student's t-test for normally distributed paired and unpaired data was used, and the Mann-Whitney or Wilcoxon test for non-parametric data, when appropriate. Data not normally distributed was analyzed by the Mann-Whitney test. Linear regression analysis using Pearson χ^2 was used to evaluate the relationship between the severity of disease in terms of functional status and LV remodelling with neurohormones and cytokines at baseline. Correlations were controlled for renal function, age and medication dosage. Linear regression was also performed to assess the relation between changes in echocardiographic parameters and plasma levels of all measured parameters that varied significantly between baseline and follow-up. For all tests, a two-tailed p value < 0.05 was considered significant.

Results

Table 1 shows the baseline characteristics of study participants. Six patients (four non-responders and two responders) commenced therapy with beta-blockers during the 1-year study period. Twenty-seven (57%) patients responded to CRT as indicated by a LVESV reduction of at least 15% (responders).

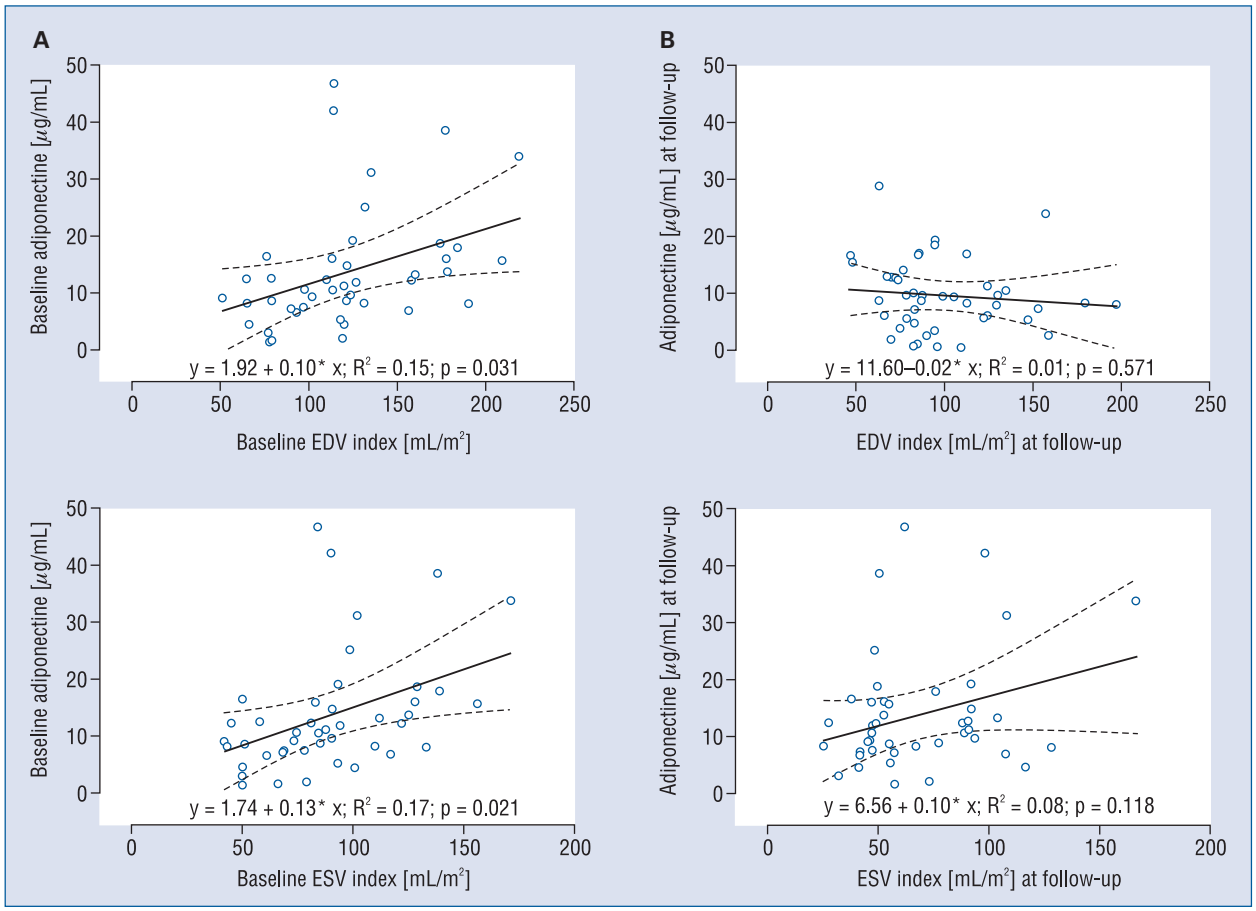

Figure 1. Correlation between adiponectin and end-diastolic volumes (EDV) and end-systolic volumes (ESV) indices at baseline (**A**) and at follow-up (**B**).

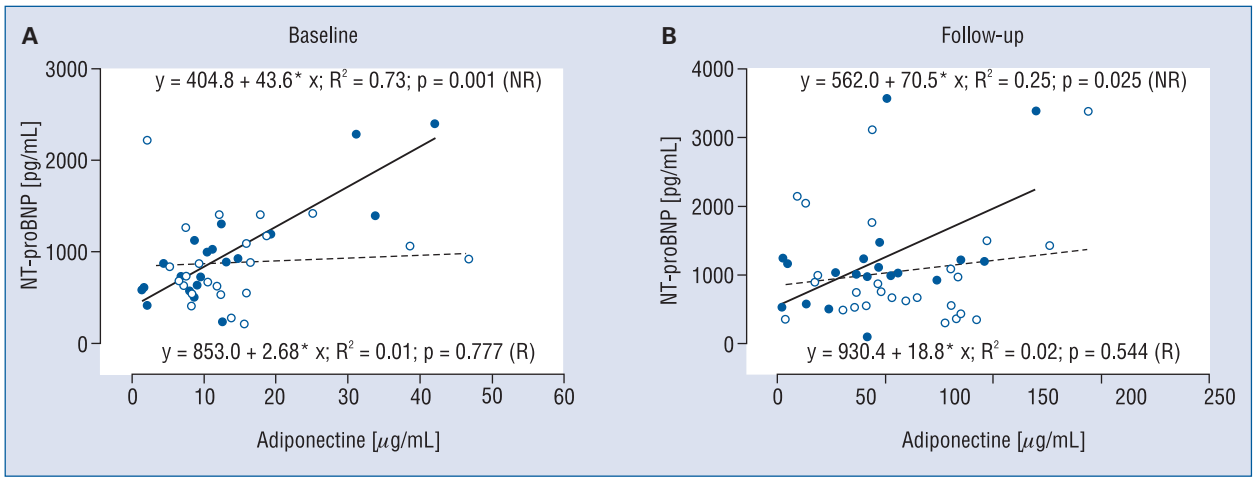

Figure 2. Correlation between adiponectin and N-terminal-pro-brain natriuretic peptide (NT-proBNP) at baseline (**A**) and at follow-up (**B**).

Baseline adiponectin levels correlated positively with end-diastolic volumes index (EDVi; $r^2 = 0.15$, $p = 0.031$) and end-systolic volumes index (ESVi; $r^2 = 0.17$, $p = 0.021$) at baseline in all study participants (Fig. 1). A positive correlation between adiponectin and NT-proBNP was detectable in non-responders both at baseline ($r^2 = 0.73$, $p < 0.001$) and at follow-up ($r^2 = 0.25$, $p = 0.025$) respectively (Fig. 2).

No correlation between adiponectin and NT-proBNP was observed among responders. Baseline plasma levels of all other measured parameters did not correlate with the CHF functional class status or LV remodelling (as indicated by LVEDVi and LVESVi modifications) even after correction for renal function, age and medication dosage. After 12 months of CRT, reduction of QRS duration ($p < 0.05$), improved functional status (as indicated by NYHA class) and QoL ($p < 0.01$ for both), and increased WT ($p < 0.01$) were observed in both responders and non-responders compared with their baseline (Table 2).

After 12 months of CRT, increased IFG-1α levels ($p = 0.019$) and decreased adiponectin and angiotensin II levels ($p = 0.029$ and $p = 0.005$, respectively) were observed in all study participants (Table 3). No significant changes in levels of norepinephrine, TNFα, sTNFR1 and sTNFR2 were observed in any participants after 12 months of CRT.

After 12 months of CRT, levels of NT-proBNP increased in non-responders ($p = 0.031$) whereas levels of angiotensin II decreased in responders ($p = 0.01$) compared with their baseline. Levels of all other measured markers of inflammation remained unchanged in responders and non-responders compared with their baseline.

Discussion

The present study examined the effect of 12 months of CRT on markers of systemic inflammation in patients with CHF. The major finding of this study is that long-term CRT decreases activation of renin–angiotensin system (RAS) in CHF patients with CRT-related reverse remodelling. In contrast, activation of RAS remained unchanged in CHF patients without reverse remodelling. Long-term CRT failed to prevent a decline in adiponectin levels in CHF patients regardless of the presence of reverse remodelling.

Levels of NT-proBNP remained unchanged in CHF patients with reverse remodelling, whereas its levels increased in those without reverse remodelling, suggesting a possible beneficial role of CRT in preventing progression of heart failure. Levels of IGF-1α increased with CRT, whereas CRT had no effect on plasma levels of ANP and inflammatory markers (TNFα, sTNFR1, sTNFR2 and IL-6).

Cardiac angiotensin formation is increased in HF [12] and angiotensin is an important modulator of cardiac remodelling in response to pathologic load or ischemic myocardial damage [13–15]. Our findings of decreased angiotensin II levels in CHF patients with CRT-related reverse remodelling corroborate these reports, since no change was observed in non-responders.

Baseline levels of adiponectin in our study were comparable with those reported previously [16, 17]. Long-term CRT was associated with a significant decline in plasma adiponectin levels in all participants, regardless of the presence of reverse remodelling. Adiponectin, a collagen-like plasma protein, with anti-inflammatory and antiatherogenic properties [18, 19] plays an important role in the development of atherosclerosis [20, 21]. Plasma concentrations of adiponectin are reduced in obesity [22], type 2 diabetes [23], hypertension [24] and coronary artery disease [17, 25].

Conversely, high adiponectin levels were predictors of mortality in HF [25]. Although the mechanisms underlying this association remain unclear, plasma levels of adiponectin appear to be predominantly regulated by cardiac natriuretic peptides such as BNP in HF [26, 27]. Recent reports suggest that BNP increases adiponectin mRNA in cultured adipocytes and that plasma levels of cGMP, a second messenger of cardiac natriuretic peptides, correlated with the plasma adiponectin levels in patients with CHF [26]. We observed a direct relation between NT-proBNP and adiponectin in the non-responder group alone. Non-responders had increased levels of NT-proBNP and a smaller decline in adiponectin levels after 1-year CRT associated with no significant changes in LV diameters.

Long-term CRT was associated with increased IGF-1α in our patients, regardless of reverse remodelling. In addition, a reduction in angiotensin II was associated with an increase in IGF-1α, corroborating the previously described inverse relationship between angiotensin II and IGF-1α in HF [28–30]. Low IGF-1α level is a risk factor for incident CHF among the elderly in the Framingham Heart Study [31]. Low-normal IGF-1α levels are associated with increased risk of acute myocardial infarction, ischemic heart disease, coronary and carotid artery atherosclerosis and stroke, as well as progression of CHF [32–34] Levels of IGF-1α are elevated in mild to moderate HF and lowered in severe symptomatic HF [35]. Three-month CRT therapy increases plasma IGF-1α levels and improves quality of life in HF, suggesting that IGF-1α may play a role as a mediator in the early phase of symptomatic improvement after CRT [28].

Levels of BNP increased in non-responders but remained unchanged in responders, suggesting a progression of HF in non-responders to CRT. Greater levels of BNP prior to implantation predict a positive response to CRT in HF [36]. Levels of

Table 2. Clinical and echocardiographic parameters.

	All participants (n = 47)			Non-responders (n = 20)			Responders (n = 27)		
	Baseline	Follow-up	P	Baseline	Follow-up	P	Baseline	Follow-up	p
QRS [ms]	147.81 ± 24.06	130.29 ± 19.92	< 0.001	145.71 ± 21.38	129.33 ± 16.68	0.05	149.44 ± 25.45	131.00 ± 22.45	0.012
NYHA	3.13 ± 0.54	2.02 ± 0.78	< 0.001	3.21 ± 0.63	1.89 ± 0.74	0.000	3.07 ± 0.47	2.12 ± 0.82	0.000
WCT [m]	258.37 ± 138.28	387.07 ± 74.34	< 0.001	275.53 ± 125.83	417.89 ± 60.15	0.001	246.30 ± 147.54	365.37 ± 76.66	0.017
QoL	34.29 ± 13.62	13.44 ± 11.58	< 0.001	39.74 ± 14.74	12.84 ± 9.50	0.000	30.31 ± 11.45*	13.88 ± 13.06	< 0.001
EDVI [mL/m^2]	114.87 ± 43.29	95.08 ± 36.08	< 0.001	118.40 ± 43.64	124.92 ± 32.77	0.208	112.26 ± 43.67	72.97 ± 18.03†	< 0.001
ESVI [mL/m^2]	83.62 ± 34.21	64.51 ± 31.47	< 0.001	87.35 ± 33.67	90.65 ± 29.35	0.276	80.85 ± 34.97	45.14 ± 14.38†	< 0.001
EF (%)	26.20 ± 5.73	32.63 ± 10.07	< 0.001	25.47 ± 6.46	29.40 ± 10.34	0.22	26.75 ± 5.14	35.05 ± 9.41†	< 0.001
Mass [g/m^2]	168.89 ± 46.91	165.72 ± 42.91	0.73	160.84 ± 42.66	175.32 ± 42.66	0.307	176.40 ± 50.85	156.76 ± 43.53	0.089
FT [ms]	344.16 ± 108.88	404.43 ± 107.12	< 0.001	327.31 ± 103.05	390.56 ± 103.05	0.054	357.00 ± 113.91	415.00 ± 87.35	0.011

*p < 0.05; †p < 0.01; WCT — walk corridor test; QoL — quality of life; EDVI — end-diastolic volume indexed; ESVI — end-systolic volume indexed; EF — ejection fraction; FT — diastolic filling time

Table 3. Serum levels of neurohormones and cytokines.

	All participants (n = 47)			Non-responders (n = 20)			Responders (n = 27)		
	Baseline	Follow-up	P	Baseline	Follow-up	P	Baseline	Follow-up	p
IGF [ng/mL]	103.29 ± 40.40	123.78 ± 54.57	0.019	106.36 ± 50.25	130.67 ± 61.73	0.072	100.99 ± 32.36	118.62 ± 49.46	0.141
TNF [pg/mL]	16.04 ± 7.01	17.03 ± 7.13	0.289	15.62 ± 3.88	15.29 ± 5.50	0.711	16.35 ± 8.75	18.33 ± 8.03	0.188
RI [ng/mL]	3.31 ± 2.00	3.41 ± 1.34	0.682	2.87 ± 1.45	3.29 ± 1.07	0.220	3.66 ± 2.32	3.51 ± 1.54	0.667
RII [ng/mL]	5.39 ± 4.74	4.63 ± 3.70	0.069	5.04 ± 4.15	4.38 ± 4.06	0.295	5.66 ± 5.25	4.82 ± 3.50	0.148
IL-6 [pg/mL]	23.95 ± 18.36	30.24 ± 20.14	0.205	21.87 ± 13.47	27.63 ± 23.55	0.458	25.87 ± 19.00	32.30 ± 17.37	0.330
Adiponectin [μg/mL]	13.75 ± 11.93	9.59 ± 7.12	0.029	13.10 ± 12.48	7.87 ± 6.30	0.062	14.31 ± 11.79	11.03 ± 7.61	0.238
Norepinephrine E [ng/mL]	0.53 ± 1.49	0.57 ± 1.50	0.664	0.29 ± 0.33	0.36 ± 0.69	0.735	0.67 ± 1.84	0.68 ± 1.81	0.784
ANP [fmol/mL]	553.97 ± 275.74	714.27 ± 412.24	0.073	428.13 ± 214.81	634.92 ± 376.09	0.132	652.84 ± 284.50	776.61 ± 442.07	0.259
NT-proBNP [fmol/mL]	107.94 ± 65.80	144.09 ± 113.22	0.030	115.02 ± 75.58	151.48 ± 117.22	0.031	102.35 ± 58.48	137.76 ± 112.79	0.210
Angiotensin II [pmol/L]	7.97 ± 7.67	4.93 ± 6.26	0.005	6.12 ± 6.85	4.75 ± 6.09	0.272	9.43 ± 8.14	5.07 ± 6.56	0.010
Aldosterone [pg/mL]	114.40 ± 68.08	84.58 ± 64.91	0.059	79.00 ± 12.51	42.65 ± 8.52	0.041	108.87 ± 59.75	93.51 ± 78.23	0.481

IGF — insulin growth factor; TNF — tumor necrosis factor; RI — TNF soluble receptor I; RII — TNF soluble receptor II; IL-6 — interleukine-6; ANP — atrial natriuretic peptide; NT-proBNP — N-terminal pro brain natriuretic peptide

ANP and BNP consistently decrease after a 3-month CRT compared with baseline [5, 7, 37]. However, the Cardiac Resynchronization-Heart Failure Trial reported a sustained reduction in levels of natriuretic peptides at 18-month follow-up, while other investigators have reported a return to baseline levels at 12-month follow-up [5, 37]. Further studies are needed to resolve the question of sustainability of CRT-related early reduction in BNP levels in HF.

Lack of effect of CRT on plasma levels of inflammatory markers such as TNFα, sTNFR1, sTNFR2 and IL-6 is in agreement with the documented no change in TNFα and IL-6 levels after three and 12 months of CRT therapy [5].

There is no established single definition of responders and non-responders after CRT therapy and the criteria of patient selection are still under debate. After publication of the PROSPECT (Predictors of Response to CRT) trial, the use of echocardiography to assess mechanical dyssynchrony and as a possible aid for selecting patients for cardiac resynchronization therapy has been criticized [38–42].

On the other hand, Yu et al. [41] documented that a reduction in LVESV of 10% was a strong predictor of lower long-term mortality and heart failure events. Recently, Ypenburg et al. [42] found that more reverse remodelling was associated with less heart failure hospitalizations and lower mortality during long-term follow-up, while the negative responder group had a markedly lower survival rate. The arguments in favour of identifying non-responders are still powerful, not only to prevent unnecessary harm to patients, but also because of the link between CRT-induced LV remodelling and mortality. Further studies are needed to identify a combination of methods able to find the site of latest mechanical activation, myocardial scar localization, and assessing venous anatomy pre-operatively, thus helping to identify those patients who would not derive any benefit from (or whose condition could potentially be worsened by) device implantation.

Conclusions

Long-term CRT is associated with decreased RAS activation and stabilization of plasma BNP levels in HF patients with reverse LV remodelling. Long-term CRT, with or without reverse LV remodelling, does not affect systemic inflammation and fails to prevent decline in plasma levels of adiponectin. Our findings underline the complexity of the interactions between the clinical effects of cardiac resynchronization, LV remodelling and the neurohormonal milieu.

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