

# The impact of cardiac resynchronization therapy on routine laboratory parameters

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**Abstract:** *Background:* Cardiac resynchronization therapy (CRT) in chronic heart failure has been shown to improve mortality and morbidity. However, comprehensive data are not available as concerns how circulating biomarkers reflecting different organ functions, such as serum uric acid, blood urea nitrogen (BUN), albumin, cholesterol, or various liver enzymes, change over time as a consequence of CRT. The aim of this prospective study was to overview these possible changes. *Methods:* A total of 20 routine laboratory parameters were measured in 122 control subjects and in 129 patients with chronic heart failure before CRT, 6 months, and 2 years later. *Results:* The levels of serum uric acid [before: 432 (331–516) mmol/L, 6-month: 372 (304–452) mmol/L, 2-year: 340 (290–433) mmol/L;  $p < 0.001$ ] and BUN [8.3 (6.4–11.5) mmol/L, 8.0 (6.3–11.1) mmol/L, 6.8 (5.0–9.7) mmol/L;  $p < 0.001$ ] reduced statistically significant. Total bilirubin underwent reduction [16 (11–23)  $\mu\text{mol/L}$ , 11 (7–14)  $\mu\text{mol/L}$ , 8 (7–13)  $\mu\text{mol/L}$ ;  $p < 0.001$ ], while albumin increased [45 (43–48) g/L, 46 (44–48) g/L, 46 (43–48) g/L;  $p = 0.04$ ]. Cholesterol concentrations elevated [4.3 (3.6–5.0) mmol/L, 4.5 (3.8–5.1) mmol/L, 4.6 (3.8–5.4) mmol/L;  $p < 0.001$ ] and glucose decreased [6.2 (5.6–7.2) mmol/L, 5.9 (5.1–6.7) mmol/L, 5.7 (5.1–6.8) mmol/L;  $p < 0.001$ ]. *Conclusions:* CRT influences the levels of routinely used biomarkers suggesting improvements in renal function, liver capacity, and metabolic changes. These changes could mirror the multiorgan improvement after CRT.

**Keywords:** chronic heart failure, resynchronization, CRT, biomarker, organic function

## Introduction

Chronic heart failure affects multiple organs other than the heart itself and should not be considered only as a reduction in pump function. It activates the immune system and induces global metabolic disturbances, which can be traced by means of various laboratory tests [1–3]. The inflammatory manifestations can be followed via the elevated C-reactive protein (CRP) levels, while the volume dysregulation leads to increases in the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) [4, 5]. A renal dysfunction is characterized by changes in creatinine, blood urea nitrogen (BUN), and uric acid levels, liver and gastrointestinal malfunctions by elevated liver enzymes and bilirubin, and decreased albumin

levels [6–11]. Metabolic changes result in hyperglycemia and hypocholesterinemia [12, 13].

Cardiac resynchronization therapy (CRT) is an effective method in chronic heart failure accompanied by ventricular dyssynchrony [14]. CRT has been shown to have anti-inflammatory effects with a decreased volume overload and an improved renal function [15–17]. Given these systemic effects, it is surprising that comprehensive data are not available as concerns how circulating biomarkers associated with organ functions, such as serum uric acid, BUN, albumin, cholesterol, or various liver enzymes, are affected by CRT as a function of time.

The aim of this prospective study was to overview these changes. We hypothesized that CRT is associated with systemic biochemical changes that correlate with echocardiographic improvement.

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## Materials and Methods

### Study population and study design

This prospective single-center observational follow-up study was designed to evaluate the prognostic impact of routinely used and novel biomarkers on the outcome of chronic heart failure patients with CRT. We previously described the role of blood count in CRT [18, 19]. This analysis focuses on the changes of routine laboratory parameters over time in the same population.

A cohort of 141 previously diagnosed and medically treated patients with chronic heart failure [New York Heart Association (NYHA) classes II–IV] with wide QRS in the ECG (>120 ms) and a severely reduced left ventricular ejection fraction (LVEF; <35%) were referred to our center between September 2009 and December 2010 for CRT implantation, according to the current guidelines [20]. The exclusion criteria included autoimmune diseases, hematologic diseases, acute or chronic inflammatory diseases, and malignancies. Four patients were excluded on this basis. The CRT involved the implantation of a left ventricular lead into the side branch of the coronary sinus, a right ventricular lead in a septal position, and a right atrial where appropriate.

Routine laboratory tests, physical examinations, and ECG and echocardiographic measurements were carried out before, 6 months, and 2 years after CRT implantation. Echocardiographic measurements were performed using the Philips iE33 system to calculate the LVEF with Simpson's method and left ventricular volumes with the Teichholz method.

In the final analysis, 129 patients with chronic heart failure were included with complete baseline laboratory and echocardiographic data. Up to a median follow-up time of 1,796 [922–2,023] days, a total of 46 patients (36%) had died.

We also analyzed the data on 122 age [67 (61–73) years], gender [82% male], and BMI [27 (24–30) kg/m<sup>2</sup>]-matched healthy [QRS: 110 (93–125) ms; LVEF: 67% (58–76)] control subjects, who participated in the voluntary Budakalász Study at our clinic [21]. The control group served to demonstrate the baseline laboratory alterations in the patients with chronic heart failure.

Prior to the enrollment, the local ethical committee at the Semmelweis University had approved the protocol, which was in accordance with the Helsinki Declaration, and all of the subjects provided their written informed consent.

The authors of this manuscript have certified that they comply with the principles of ethical publishing in *Interventional Medicine & Applied Science*: Szél Á, Merkely B, Hüttl K, Gál J, Nemes B, Komócsi A: Statement on ethical publishing and scientific authorship. *IMAS* 2, 101–102 (2010).

### Laboratory measurements

Serum samples for routine laboratory measurements at baseline, and at 6 months and 2 years after implantation were collected and analyzed with the Cobas Integra 400 Plus<sup>®</sup> (Mannheim, Germany) clinical chemistry system using absorbance photometric and turbidimetric techniques. The following Roche Diagnostics (Mannheim, Germany) reagents were used: creatine kinase (CK); creatine kinase MB isoenzyme (CKMB); creatinine; uric acid; BUN; CRP; glutamic oxaloacetic transaminase (GOT); glutamic pyruvate transaminase (GPT); gamma-glutamyl transferase (GGT); alkaline phosphatase (ALP); lactate dehydrogenase (LDH); total bilirubin; total protein; albumin; cholesterol; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); and glucose.

Aliquots for NT-proBNP were processed within 2 h of sampling and were stored frozen at –80 °C until the measurements. NT-proBNP levels were measured through electrochemiluminescence with a Cobas e 411<sup>®</sup> analyzer (Mannheim, Germany) using Roche Elecsys NT-proBNP II kits (Cat. no.: 04842464190, Mannheim, Germany).

**Table I** | Baseline parameters of the patients with chronic heart failure

Age (years)	67 (60–73)
Male gender	105 (81)
Body mass index (kg/m <sup>2</sup> )	27 (24–30)
Ischemic etiology	74 (57)
Left bundle branch block	107 (82)
CRT-D	21 (16)
Optimal lead position	94 (72)
QRS (ms)	160 (150–180)
LVEF (%)	27 (23–33)
LVESV (mL)	210 (154–268)
LVEDV (mL)	303 (242–351)
NYHA III–IV	111 (86)
Hypertension	71 (55)
Diabetes mellitus	47 (36)
Angiotensin convertase inhibitor	123 (95)
Beta-blocker	115 (89)
Mineralocorticoid receptor inhibitor	92 (71)
Loop diuretics	101 (78)

Data are expressed as medians with interquartile ranges for continuous variables and as event numbers with percentages for categorical variables. CRT-D = cardiac resynchronization therapy with an implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVEDV = left ventricular end diastolic volume; NYHA III–IV = New York Heart Association classification III–IV. N = 129

Statistical analysis

The data presented in this analysis deviated from normal distribution (tested by the Shapiro–Wilk test), and the data are therefore expressed as medians with interquartile ranges (25th percentile to 75th percentile), or as percentages with event numbers. A two-tailed *p* value of <0.05 was considered statistically significant in all cases. The statistical analysis was carried out using GraphPad Prism 6.03 (GraphPad Software Inc., USA) software.

The Mann–Whitney test was used for independent group comparisons. Dependent groups were assessed by the Friedman test with Dunn *post-hoc* analysis. The Spearman correlation was calculated.

Results

Baseline characteristics

The baseline characteristics of the 129 patients are displayed in Table I. The majority of the patients were male (81%), had ischemic etiology (57%) and a poor functional status (NYHA III–IV: 86%), and were on optimal medication.

Their ECGs displayed a wide QRS [160 (150–180) ms] and left bundle branch block morphology in 83% of the cases.

Echocardiographic changes

The CRT led to the LVEF being increased statistically significant after 6 months [27% (23–33) vs. 37% (31–41), *p* < 0.001], while the left ventricular end systolic volume (LVESV) [210 (153–267) mL vs. 167 (111–234) mL, *p* < 0.001] and left ventricular end diastolic volume (LVEDV) [303 (242–351) mL vs. 259 (202–315) mL, *p* < 0.001] were decreased. No further significant improvement was seen at the 2-year follow-up in the LVEF [42% (32–48) mL, *p* = 0.05], LVESV [160 (109–212) mL, *p* = 0.57], and LVEDV [242 (195–305) mL, *p* = 0.60]. However, the improvement still persisted (baseline vs. 2 years, *p* < 0.001).

Changes in cardiac biomarkers

Figure 1 demonstrates the changes in cardiac laboratory parameters. Compared with the healthy controls, the

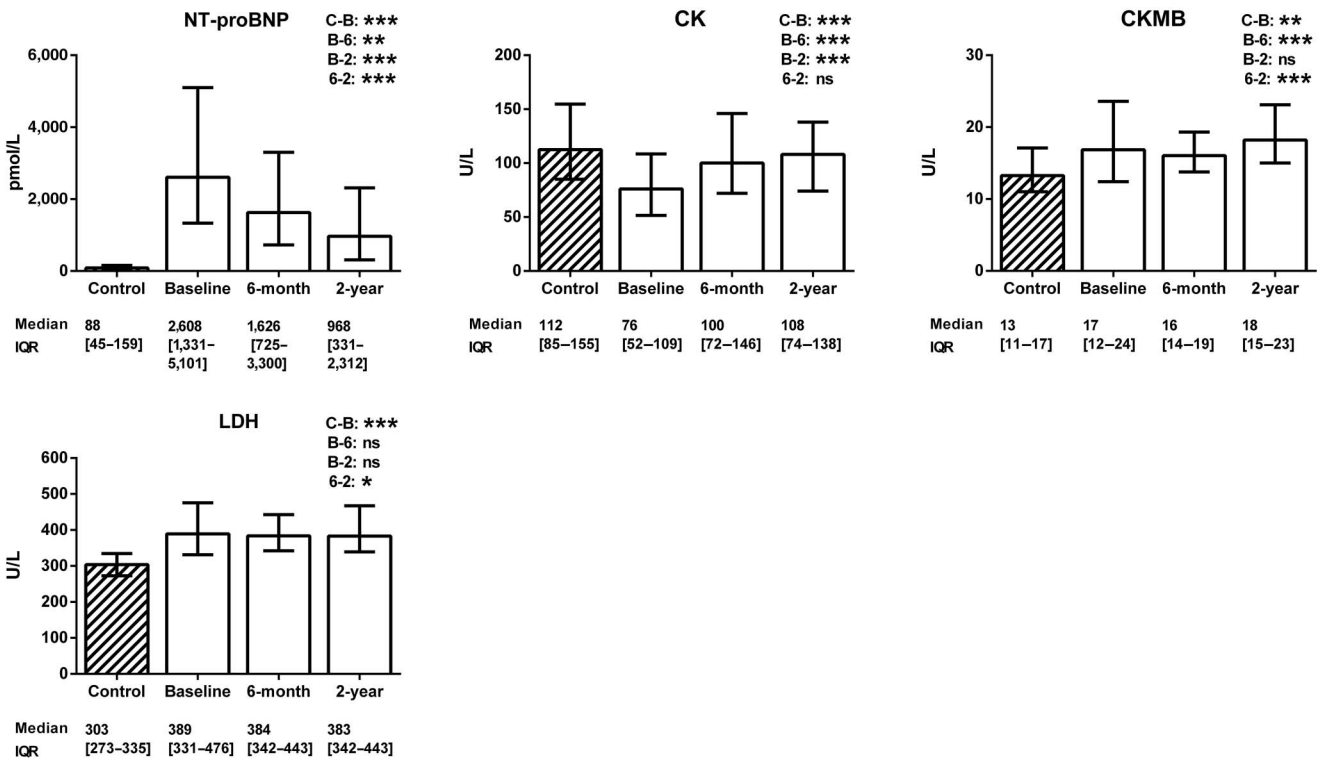


Fig. 1. Changes in cardiovascular biomarkers. The data are expressed as medians with interquartile ranges (IQR). The Mann–Whitney test was used for the comparison of the healthy control group (striated column) with the patients with chronic heart failure (blank columns). The changes in the cardiovascular biomarkers of the patients with heart failure after cardiac resynchronization therapy were assessed using the Friedman test with Dunn *post-hoc* analysis (C = control level, B = baseline level, 6 = 6-month level, and 2 = 2-year level). NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; CK = creatine kinase; CKMB = creatine kinase MB isoenzyme; LDH = lactate dehydrogenase. *N* (control) = 122; *n* (baseline) = 129; *n* (6-month) = 105; *n* (2-year) = 83. \*0.01 ≤ *p* < 0.05; \*\*0.001 ≤ *p* < 0.01; \*\*\**p* < 0.001; ns = not significant

patients with chronic heart failure presented with elevated NT-proBNP, CKMB, and LDH ( $p < 0.001$ ), but with a decreased CK level ( $p < 0.001$ ). Two years after CRT, the NT-proBNP concentration was decreased and the CK level was increased ( $p < 0.001$ ), while the CKMB and LDH levels remained statistically unchanged ( $p = 0.99$  and  $p = 0.26$ , respectively).

The change in NT-proBNP after 6 months correlated well with those in the LVEF ( $r = -0.26$ ,  $p = 0.006$ ), LVESV ( $r = 0.37$ ,  $p < 0.001$ ), and LVEDV ( $r = 0.28$ ,  $p = 0.003$ ). The change in NT-proBNP after 2 years also correlated with those in the LVEF ( $r = -0.42$ ,  $p < 0.001$ ), LVESV ( $r = 0.50$ ,  $p < 0.001$ ), and LVEDV ( $r = 0.55$ ,  $p < 0.001$ ). Additionally, the change in CK after 2 years correlated with those in the LVESV ( $r = 0.34$ ,  $p = 0.009$ ) and LVEDV ( $r = 0.37$ ,  $p = 0.004$ ). No other statistically significant correlations were observed (data not shown).

*Changes in renal and inflammatory parameters*

Figure 2 reflects the significant elevations in both renal (creatinine, uric acid, and BUN) and inflammatory (CRP and total protein) markers in the patients with chronic heart failure before CRT ( $p < 0.001$ ). The renal

improvement at 2 years following CRT was characterized by decreases in creatinine ( $p = 0.03$ ), uric acid ( $p < 0.001$ ), and BUN ( $p = 0.008$ ). The anti-inflammatory potential of the CRT was suggested by the reductions in CRP ( $p = 0.03$ ) and total protein ( $p < 0.001$ ).

The change in the serum creatine level at 6 months was associated with an LVESV improvement ( $r = 0.24$ ,  $p = 0.01$ ), while the change in uric acid was followed by an LVEF recovery ( $r = -0.17$ ,  $p = 0.04$ ). The change in the BUN level at 2 years correlated with the ventricular reverse remodeling (LVESV:  $r = 0.23$ ,  $p = 0.06$  and LVEDV:  $r = 0.29$ ,  $p = 0.02$ ). The change in CRP at 2 years paralleled the LVEF improvement ( $r = -0.22$ ,  $p = 0.04$ ).

*Changes in hepatic markers*

Figure 3 reveals that the baseline levels of liver enzymes (GOT, GPT, and GGT) and total bilirubin were elevated ( $p < 0.001$ ), while those of ALP were not ( $p = 0.14$ ), and the level of albumin ( $p = 0.04$ ) was reduced in the patients with chronic heart failure. At 2 years after the CRT, the levels of GOT, GPT, and GGT decreased significantly ( $p < 0.001$ ), that of ALP was unchanged ( $p = 0.99$ ) and that of albumin was increased ( $p = 0.006$ ).

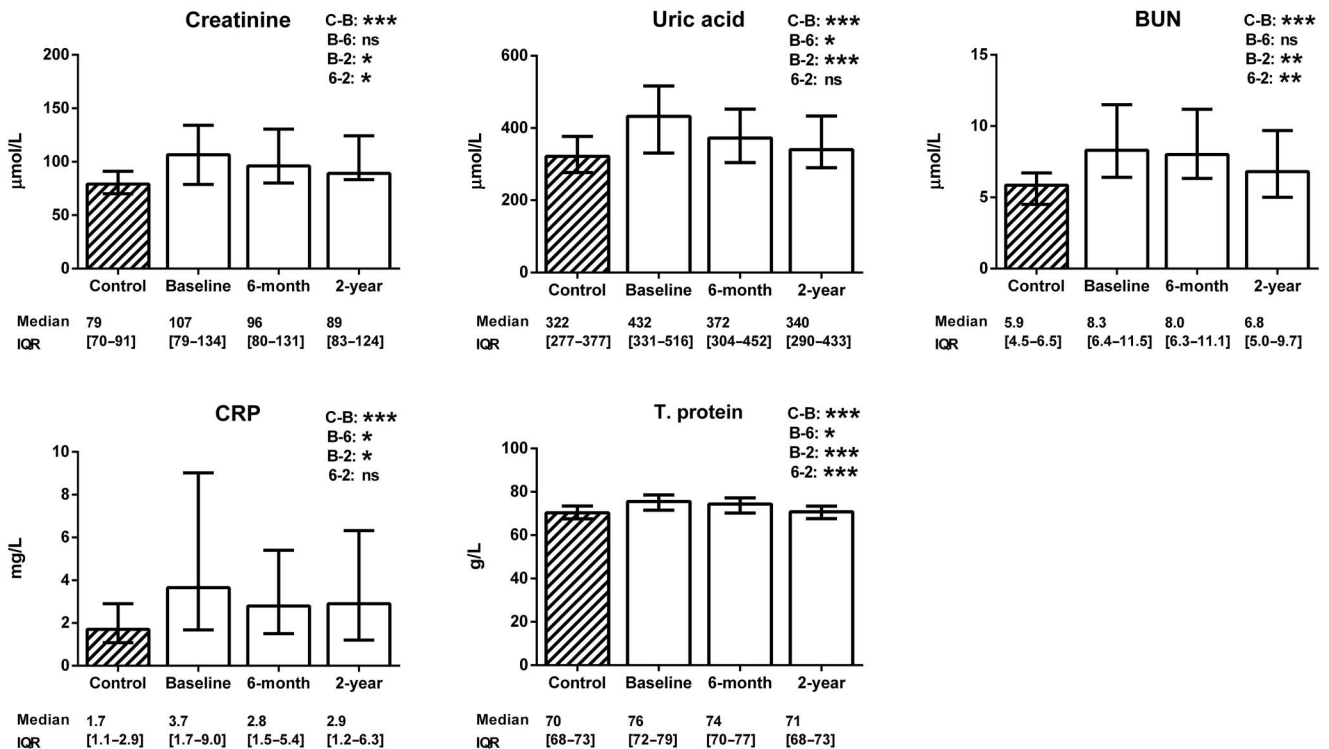
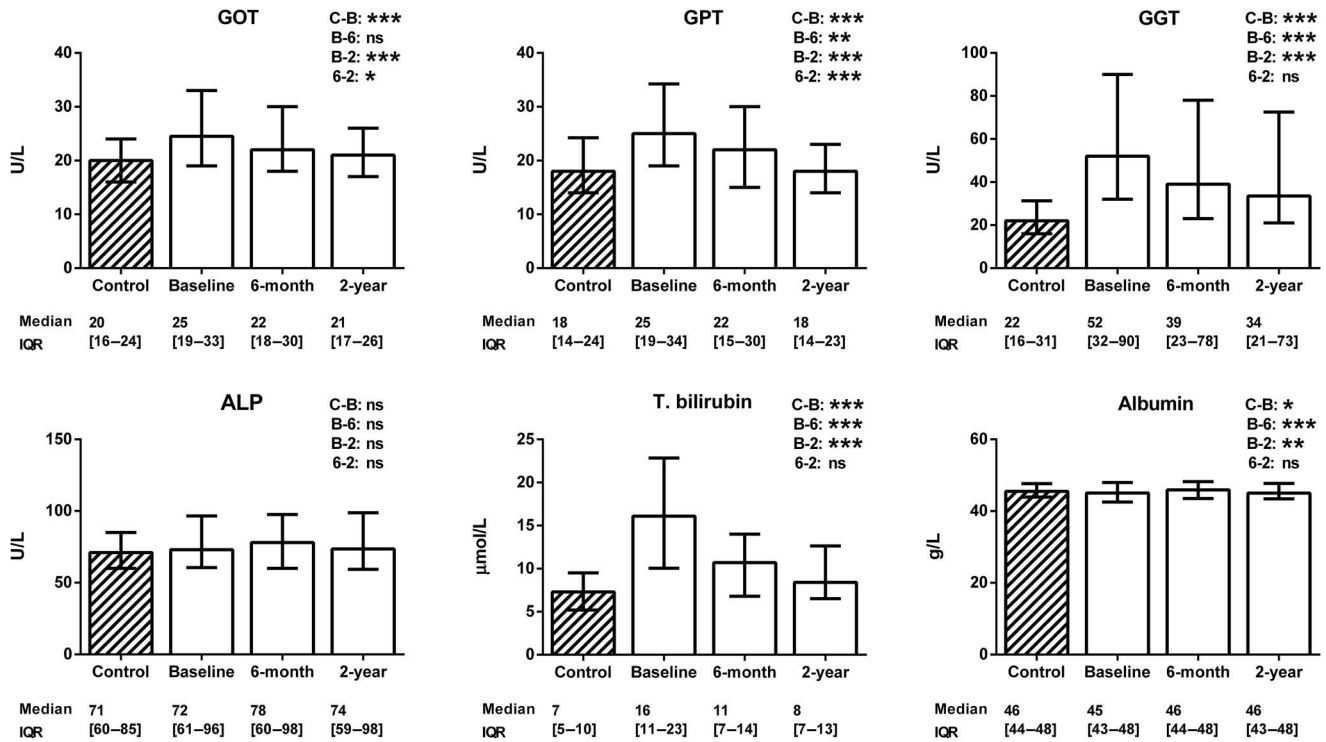


Fig. 2. Changes in renal and inflammatory parameters. The data are expressed as medians with interquartile ranges (IQR). The Mann-Whitney test was used for the comparison of the healthy control group (striated column) with the patients with chronic heart failure (blank columns). The changes in renal and inflammatory parameters of the patients with heart failure after cardiac resynchronization therapy were assessed using the Friedman test with Dunn *post-hoc* analysis (C = control level, B = baseline level, 6 = 6-month level, and 2 = 2-year level). BUN = blood urea nitrogen; CRP = C reactive protein; T. protein = total protein.  $N$  (control) = 122;  $n$  (baseline) = 129;  $n$  (6-month) = 105;  $n$  (2-year) = 83.  $*0.01 \leq p < 0.05$ ;  $**0.001 \leq p < 0.01$ ;  $***p < 0.001$ ; ns = not significant



**Fig. 3.** Changes in hepatic markers. The data are expressed as medians with interquartile ranges (IQR). The Mann–Whitney test was used for comparison of the healthy control group (striated column) with the patients with chronic heart failure (blank columns). The changes in gastrointestinal markers of the patients with heart failure after cardiac resynchronization therapy were assessed by using the Friedman test with Dunn *post-hoc* analysis (C = control level, B = baseline level, 6 = 6-month level, 2 = 2-year level). GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvate transaminase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase; T. bilirubin = total bilirubin. N (control) = 122; n (baseline) = 129; n (6-month) = 105; n (2-year) = 83. \*0.01 ≤ p < 0.05; \*\*0.001 ≤ p < 0.01; \*\*\*p < 0.001; ns = not significant

Of the hepatic parameters, the GGT change at 2 years correlated with the change in the LVEF ( $r = -0.32$ ,  $p = 0.005$ ).

#### Changes in metabolic parameters

As regards the baseline metabolic parameters, the patients had low levels of lipoproteins (cholesterol, triglyceride, HDL, and LDL), but a high glucose concentration ( $p < 0.001$ ), as demonstrated in Fig. 4. Following implantation, the levels of lipoproteins increased ( $p < 0.001$ ), while those of the glucose decreased over time ( $p = 0.01$ ).

The triglyceride changes correlated with reductions in the left ventricular volumes at 2 years (LVESV:  $r = -0.22$ ,  $p = 0.06$  and LVEDV:  $r = -0.33$ ,  $p = 0.005$ ).

## Discussion

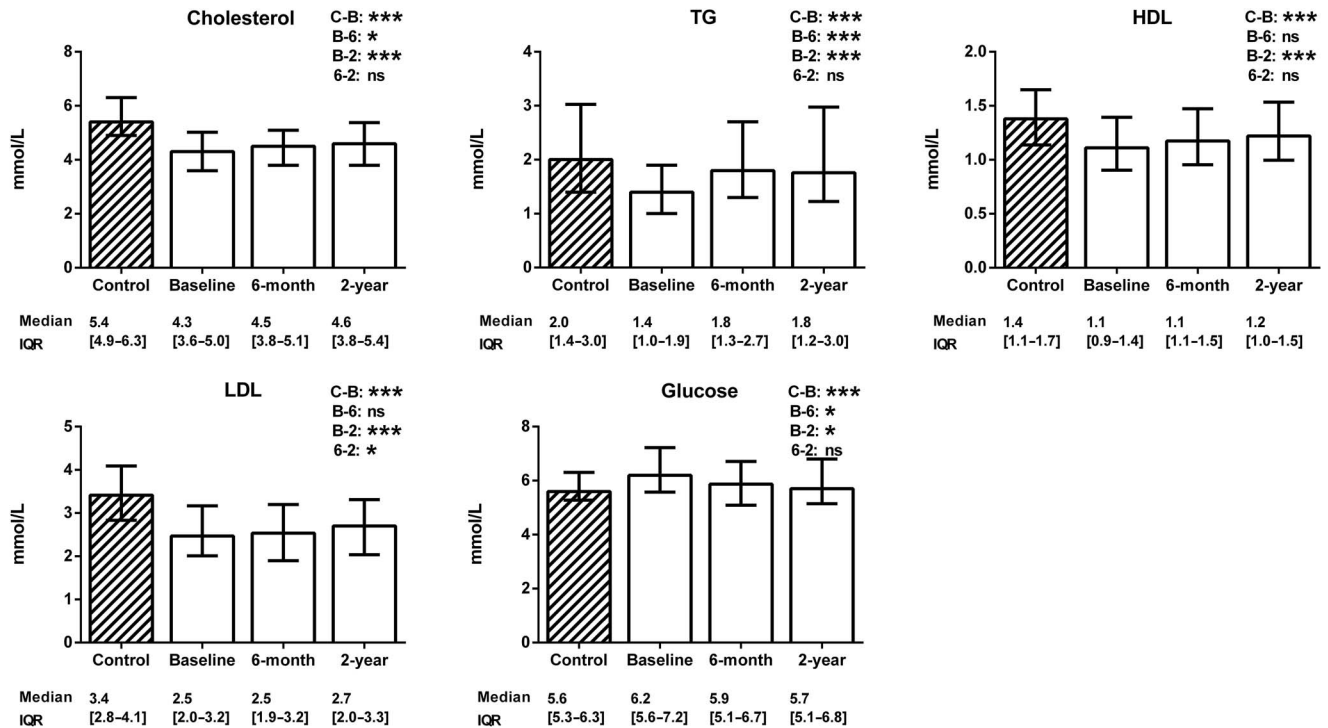
### Synopsis of the key findings

We found that the patients with chronic heart failure who presented for CRT displayed cardiac congestion, tissue

damage, signs of inflammatory activation, impaired renal and liver functions, low lipoprotein levels, and a high glucose concentration. CRT resulted in echocardiographic reverse remodeling, which persisted up to 2 years, with accompanying improvements in renal function, liver capacity, and metabolic changes.

### Possible mechanisms and explanations

The results of this study confirm previous findings relating to the laboratory changes in chronic heart failure and the effects of CRT. The systemic inflammation and oxidative stress result in hyperglycemia, while the ongoing inflammation drives the elevations in CRP and total protein [1–4, 13]. The lipoproteins buffer the inflammatory cytokines and endotoxins, and the chronic inflammation therefore decreases the cholesterol level [12]. The release of catecholamines and sympathetic activation lead to a volume overload and redistribution [1–3]. The volume overload enhances NT-proBNP production, dilates the ventricles, and causes cardiac tissue damage and remodeling, resulting in increased levels of CKMB and LDH [5]. As one of the characteristic features of chronic heart failure is



**Fig. 4.** Changes in metabolic parameters. The data are expressed as medians with interquartile ranges (IQR). The Mann-Whitney test was used for comparison of the healthy control group (striated column) with the patients with chronic heart failure (blank columns). The changes in metabolic parameters of the patients with heart failure after cardiac resynchronization therapy were assessed by using the Friedman test with Dunn *post-hoc* analysis (C = control level, B = baseline level, 6 = 6-month level, 2 = 2-year level). TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein.  $N(\text{control}) = 122$ ;  $n(\text{baseline}) = 129$ ;  $n(6\text{-month}) = 105$ ;  $n(2\text{-year}) = 83$ . \* $0.01 \leq p < 0.05$ ; \*\*\* $p < 0.001$ ; ns = not significant

reduced mitochondrial energy production in both the cardiac and the skeletal muscle, a creatine phosphate deficit develops with low CK activity and a consequently reduced serum level [22]. On the other hand, the volume redistribution decreases the renal and gastrointestinal blood flows [23]. The consequent liver dysfunction is reflected by elevated levels of liver enzymes and total bilirubin, and decreased albumin production, while the renal dysfunction is characterized by increases in the levels of serum creatinine, uric acid, and BUN [6–8, 10, 11, 23, 24].

This was the first study that demonstrates how CRT affects these routinely used biomarkers and the correlations between the echocardiographic and laboratory changes. CRT exerts reverse remodeling and improves the cardiac function [25]. As the cardiac output increases, the volume overload and redistribution decrease [26]. The release of NT-proBNP lessens, while the level of CK increases, and those of CKMB and LDH remain elevated, because reverse remodeling is an active process with tissue regeneration and a functional mitochondrial improvement [26–28]. The volume distribution improves, and the renal blood flow and filtration are restored, and consequently, the excretion of creatinine, uric acid, and BUN is enhanced and the serum levels decrease [15, 16]. The

better gastrointestinal circulation is mirrored by the decreases in liver enzymes and total bilirubin and the restored albumin production. The inflammatory processes resolve, the levels of CRP and total protein decrease, and the lipoproteins undergo a process of unbinding and their levels are elevated [29].

#### Strengths and limitations

The main strength of this study is the overview of routinely used biomarker changes in CRT, with the use of a matched healthy control group. A possible limitation could be the relatively small sample size. This analysis should be considered as hypothesis generating and preliminary, and larger trials are needed to confirm our results.

#### Conclusions

This study has revealed how serum biomarkers can mirror the multiorgan improvement after CRT. We found that patients with chronic heart failure presenting for CRT exhibited cardiac congestion, tissue damage and

steady-state inflammation, impaired renal and liver functions, low lipoprotein levels, and a high glucose concentration. CRT resulted in echocardiographic reverse remodeling, which persisted up to 2 years. These changes were followed by improvements in the renal function, the liver capacity, and metabolism.

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**Authors' contribution:** AMB and PP: conception and design of the research, acquisition of data, statistical analysis and interpretation, drafting of the manuscript, and critical revision. KVN, AA, ZB, LM, TT, DB, and LG: acquisition of data and critical revision. EZ: conception and design of the research, acquisition of data, and critical revision. BM: conception and design of the research, acquisition of data, obtaining funding and supervising the work, and critical revision. GS: conception and design of the research, acquisition of data, statistical analysis and interpretation, drafting of the manuscript, obtaining funding and supervising the work, and critical revision. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AMB and PP equally contributed to the work and they should be considered as first authors of the article. BM and GS equally contributed to the work and they should be considered as last authors of the article.

**Conflict of interest:** None declared.

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