Cardiol Cardiovasc Med 2019; 3 (2): 020-029 *DOI: 10.26502/fccm.92920050*

Research Article

The Importance of Renal Function in Evaluating Response to Resynchronisation Therapy in Patients with Heart Failure after Implantation of Cardiac Resynchronisation Therapy and Defibrillator

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Received: 02 March 2019; **Accepted:** 11 March 2019; **Published:** 13 March 2019

Abstract

Cardiac resynchronisation therapy (CRT) has a well-established position as one of the forms of treatment of selected groups of patients with heart failure (HF). Unfortunately, according to different data from the literature, the percentage of patients not responding to treatment using CRT remains consistently high and is estimated at around 20% to nearly 50%, according to the accepted definition of response to resynchronisation therapy. The aim of our work is to assess the impact of renal function in evaluating the response to resynchronisation therapy in a 12-month observation. The study included 46 patients with heart failure meeting the criteria and qualified for implantation of cardiac resynchronisation therapy and defibrillator (CRT-D), hospitalized in the Department of Interventional Cardiology and Cardiac Arrhythmias of the Medical University of Lodz. A responder to CRT was defined as a person who lived a certain time of observation with no episodes of HF exacerbation and improved his/her physical fitness referring to a decline in functional class by at least 1 degree according to the NYHA. In our study we determined empirical cut-off points for initial concentrations of creatinine and GFR-MDRD which can predict positive therapeutic response to CRT. The effect of resynchronisation therapy on improving kidney function remains debatable and requires further research.

Keywords: Cardiac resynchronisation therapy; Chronic heart failure; Chronic kidney disease

1. Introduction

Resynchronisation therapy (CRT) has a well-established position, supported by the results of randomized research works, as one of the forms of treatment of selected groups of patients with heart failure (HF). It is designed to improve

the prognosis, quality of life, physical fitness, and alleviate the symptoms of the disease. Unfortunately, according to different data from the literature, the percentage of patients not responding to treatment using CRT remains consistently high and is estimated at around 20% to nearly 50%, according to the accepted definition of response to resynchronisation therapy [1]. Attempts to identify the factors predisposing the best response to resynchronisation therapy persuade next researchers to formulate different, based on different criteria, definitions of response to resynchronisation therapy, taking into account clinical, laboratory, electrocardiographic, functional and echocardiographic data. This is one of the biggest challenges of modern cardiology, because heart failure became a major, multidimensional and socio-economic health problem. There will be no exaggeration to say that today it has reached epidemic dimensions. Alarming statistics attest to the ever increasing number of patients with HF. The prognosis of this disease entity remains very bad. Epidemiological data shows that 50% of patients dies within 5 years from diagnosis, what makes the 5-year survival rate of patients with HF worse than in people with cancer (with the exception of lung cancer) [2]. The aim of our work is to assess the impact of renal function in evaluating the response to resynchronisation therapy in a 12-month observation.

2. Methods

2. 1 The study group

The study included 46 patients with heart failure meeting the criteria and qualified for implantation of cardiac resynchronisation therapy and defibrillator (CRT-D), hospitalized in the Department of Interventional Cardiology and Cardiac Arrhythmias, Medical University of Lodz. The inclusion criteria were: (1) optimal pharmacotherapy of heart failure, (2) chronic heart failure in II-III functional class according to the NYHA, (3) the QRS complex duration time ≥120 ms, (4) systolic dysfunction of LV with ejection fraction (EF) ≤ 35%. The exclusion criteria were: (1) exacerbated heart failure (2) advanced chronic lung disease, (3) infectious diseases with pyrexia during the last three weeks. A responder to CRT is defined as a person who lived a certain time of observation with no episodes of exacerbation of HF and improved his/her physical fitness referring to a decline in functional class by at least 1 degree, according to the NYHA. The analysis of the data collected was carried out before the implantation of CRT-D and in the subsequent time points of follow-up, i.e., after the 1st, 3rd, 6th and12th month.

2. 2 Demographic and clinical data analysis

Each patient underwent anamnesis along with assessment of NYHA functional class, and physical examination. The subject of statistical analysis were also demographic data (age, gender) and data from the anamnesis considering the aetiology of HF and comorbidities such as: arterial hypertension, type 2 diabetes mellitus, a history of stroke or transient ischemic attack (TIA), atrial fibrillation, chronic kidney disease, episodes of sudden cardiac arrest and persistent ventricular tachycardia.

2. 3 Laboratory tests

All the patients were performed laboratory tests by collecting blood samples from the basilic vein. Analyses were made both prior to the implantation of the CRT-D system, and in the subsequent time points of follow-up, i.e. after 1, 3, 6

and 12 months from the implementation of the procedure.

Biochemistry was carried out using the Beckman Coulter AU680 biochemical analyser, and immunochemistry-using the COBAS e 411 immunochemical analyser (Roche Diagnostics). The test results were interpreted on the basis of reference values provided by the laboratory.

In each patient the following laboratory analysis was performed:

1. Concentration of creatinine-kinetic method with alkaline picrate; reference range-58-96 µmol/l
2. GFR-MDRD-glomerular filtration rate calculated from the modification of diet in renal dysfunction (MDRD) formula:

   GFR-MDRD (ml/min/1.73m^2) = 170 × A$^{-0.999}$ × age$^{-0.176}$ × B$^{-0.17}$ × C$^{-0.318}$ × 0.762 [22]

   where A-serum concentration of creatinine in mg% (µmol/L/88.4); B-serum concentration of urea nitrogen (BUN) in mg% (mmol/l × 2.8); C-concentration of albumins in mg/L (g/L × 0.1) the coefficient of 0.762 was used in women.

Obtaining the result of GFR permitted to determine the stage of chronic kidney disease in the studied patients on the basis of the Kidney Disease Outcome Quality Initiative (KDOQI) classification, 2012 [3].

2. 4 Statistical analysis

In the course of the descriptive analysis of non-measurable (qualitative) data the results were presented in the form of absolute numbers and percentages (%). Measurable (quantitative) traits were described using the mean (M) and standard deviation (SD) values. In the statistical analysis, we used the $\chi 2$ test of independence, Fisher's exact test, analysis of variance (ANOVA) with repeated measurements or Friedman's analysis of variance test (in the absence of normal distribution and homogeneity of variance), ANOVA without replication or the Mann-Whitney rank-sum U test (in the absence of normal distribution and homogeneity of variance), as well as generalized linear models with repeated measurements. In order to determine an empirical cut-off point for selected biochemical parameters-i.e., to diversify the study subjects in groups of responders vs. non-responders-a ROC curve (receiver operating characteristic) was plotted and area under the ROC curve was calculated (AUC), as well as sensitivity and specificity values were given for the cut-off points obtained in this procedure. A level of $p<0.05$ was considered statistically significant. To perform the statistical analyses, we used the Stata®/Special Edition, release 14.1 software package (StataCorp LP, College Station, Texas, USA).

3. Results

The study group accounted for 46 patients (76%-men) with implanted CRT-D and with the mean age of 64 ± 8 years. The criteria for response to cardiac resynchronisation therapy, adopted in the study, were met by 26 patients, i.e. 56. 5%. The study groups differed significantly in terms of aetiology of HF-non-ischemic cardiomyopathy was significantly more common among the responders, unlike non-responders in whom dominated the ischemic aetiology of HF ($p=0.001$). Patients assigned to the group of responders were significantly younger than the non-responders

(p=0.03). Based on the characteristics of the surveyed groups, there was observed significantly increased prevalence of selected coexisting diseases among the non-responders such as: type 2 diabetes mellitus (p=0.01), a history of atrial fibrillation (AF) and stroke/TIA (p=0.001), kidney failure (based on anamnesis; p=0.03), as well as episodes of VT (p=0.01). In the group of patients with AF, 3 patients had a persistent form of arrhythmia with good control of rhythm (2 patients after radiofrequency ablation of the atrioventricular junction; the percentage of biventricular pacing exceeded 98%). In the remaining patients paroxysmal AF was diagnosed. A clear statistical significance between the analysed groups of patients was shown considering the QRS complex morphology before the implantation of CRT-D- among the responders the presence of LBBB dominated, while in the group of non-responders-did the RBBB and IVCD (Table 1).

Analysed trait	**Overall**		**Responders**		**Non-responders**		**Statistical significance***
	n	**%**	**n**	**%**	**n**	**%**	
Response to CRT							
Responders	26	56.5	-	-	-	-	-
Non-responders	20	43.5	-	-	-	-	-
Studied patients' gender							
Males	35	76.1	19	73.1	16	80.0	0.4
Females	11	23.9	7	26.9	4	20.0	
Aetiology of HF							
DCM	24	52.2	17	65.4	7	35.0	0.001
Non-DCM	22	47.8	9	34.6	13	65.0	0.001
Comorbidities							
AH	22	47.8	11	42.3	11	55.0	0.1
T2D	20	43.5	9	34.6	11	55.0	0.01
Stroke or TIA	5	10.9	1	3.9	4	20.0	0.001
AF	11	23.9	3	11.5	8	40.0	0.001
After SCA	4	8.7	3	11.5	1	5.0	0.2
After VT	4	8.7	1	3.9	3	15.0	0.01
ADS	1	2.2	0	0.00	1	5.0	0.4
History of renal insufficiency	8	17.4	3	11.5	5	25.0	0.03
Occurrence of LBBB	33	73. 3	22	88.0	11	55.0	0.001
Occurrence of RBBB	5	11.4	1	4.0	4	21.1	0.001
Occurrence of IVCD	9	20.4	2	8.0	7	36.8	0.001

*responders vs. non-responders

ADS-alcohol dependence syndrome; AF-arterial fibrillation; AH-arterial hypertension; DCM-dilated cardiomyopathy; non-DCM-non-dilated cardiomyopathy; HF-heart failure; IVCD-intraventricular conduction delay; LBBB-left bundle

branch block; RBBB-right bundle branch block; SCA-sudden cardiac arrest; TIA-transient ischemic attack; T2D-type 2 diabetes mellitus; VT-ventricular tachycardia.

Table 1: Characteristics of the study group at baseline (discrete variables).

Mean initial values of selected laboratory parameters, such as the concentration of creatinine, NT-proBNP, cTnT hs and GFR-MDRD, did not statistically significantly differentiate the study participants (Table 2). During the 12-month follow-up, there was reported a total of 16 episodes of exacerbation of HF (three incidents in the 1st and 6th month, and 5-in the 3rd and 12th month of follow-up, respectively); 2 patients died-the cause of death was not linked to the progression of HF. The evaluation of laboratory parameters was performed in two ways: the relevant values were analyzed in subsequent time points of follow-up in the responders and the non-responders separately, as well as the results obtained were compared between the two study groups.

Analysed trait	**Oveerall**		**Responders**		**Non-responders**		**Statistical significance***
	M	**SD**	**M**	**SD**	**M**	**SD**	
Age (years)	64	8	62	8	66	7	0.03
QRS wave width (ms)	151	24	153	25	149	22	0.9
NT-proBNP (pg/ml)	4796	6228	3768	4160	6080	8052	0.4
cTnT-hs (ng/ml)	0.039	0.064	0.025	0.018	0.055	0.090	0.5
Creatinine (µmol/l)	112	27	105	25	120	28	0.1
GFR (ml/min/1. 73 m^2)	60	17	66	13	53	19	0.1

*responders vs. non-responders

cTnT-hs-high sensitivity cardiac troponin T; GFR-MDRD-glomerular filtration rate, modification of diet in renal dysfunction; M-mean; NT-proBNP-N-terminated B-type natriuretic peptide; SD-standard deviation

Table 2: Characteristics of the study group at baseline (numerical variables).

The statistical analysis of the mean concentrations of creatinine during the 12-month follow-up showed no significant changes in both study groups. It draws attention to the fact that initially, and during the whole of follow-up, the mean concentrations of creatinine exceeded the reference values. In the group of non-responders there were observed higher creatinine values in comparison to the group of responders, and they acquired the statistical significance in the 3rd month (p=0.04) and, in particular, in the 12th month (p=0.02) of follow-up, when the concentration of creatinine was significantly higher in the group of responders (139 ± 78 µmol/l vs. 100 ± 23 µmol/) (Figure 1A). An empirical cut-off point for the concentration of creatinine, equal to 101 µmol/l, was calculated, which, with high sensitivity (75%) and more than 54% of specificity, predicted a positive response to resynchronisation therapy (PPV-57.7%, NPV-72.2%; area under the ROC curve-AUC=0.637) (Figure 1B).

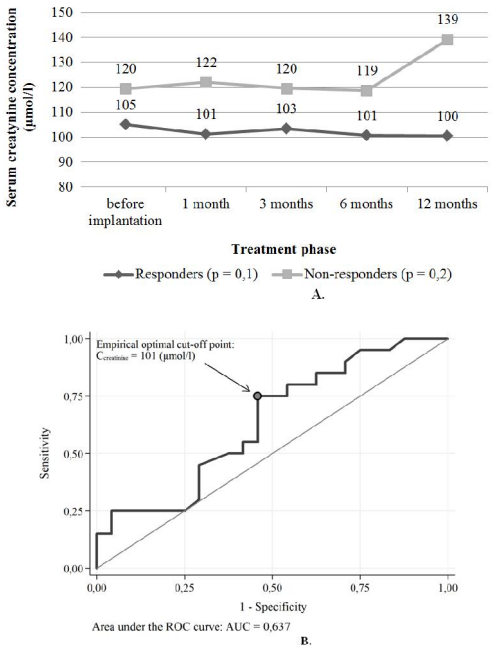

Figure 1: (A). Mean concentrations of creatinine in blood serum (µmol/l) in the studied patients before (p=0.1) and after 1 (p=0.1), 3 (p=0.04), 6 (p=0.06) and 12 months (p=0.02) from the implantation of CRT-D, with the division into responders and non-responders; (B). ROC curve along with an empirical cut-off point for the concentration of creatinine in blood serum (µmol/l) before CRT, in the context of the prediction of therapeutic response.

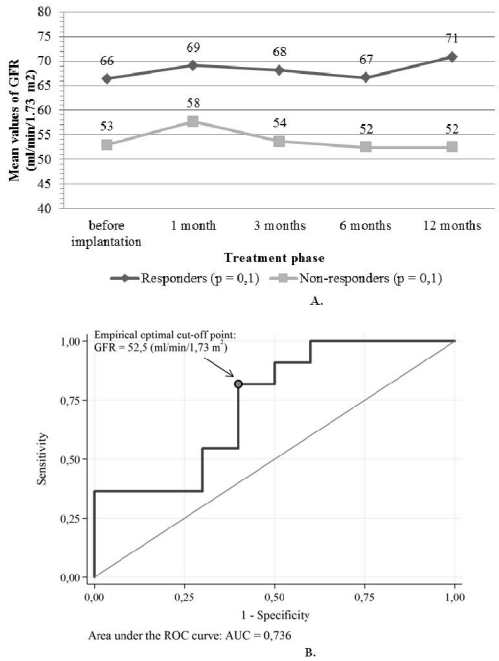

Figure 2: (A). Mean values of GFR (ml/min/1.73 m^2) in the studied patients before (p=0.1) and after 1 (p=0.2), 3 (p=0.1), 6 (p=0.03) and 12 months (p=0.01) from the implantation of CRT-D, with the division into responders and non-responders; (B). ROC curve along with an empirical cut-off point for GFR (ml/min/1.73 m^2) before CRT, in the

context of the prediction of therapeutic response.

Similar conclusions were drawn regarding the analysis of the estimated glomerular filtration rate-GFR-MDRD. There were no statistically significant differences regarding the mean values of GFR-MDRD, assessed separately within the group of responders and non-responders. All the patients presented reduced values of GFR-MDRD, which allowed to determine the stage of chronic kidney disease (CKD)-in the group of responders-at stage 2, and in the group of non-responders–at stage 3 of CKD. There were shown statistically significant differences in the values of GFR-MDRD between the study groups in the 6^{th} (p=0.03) and 12^{th} month (p=0.01) of follow-up (Figure 2A). An empirical cut-off point for the GFR-MDRD also was set; it equaled to 52.50 ml/min/1. 73 m^2 and, with nearly 82% sensitivity and 60% specificity, predicted a positive response to resynchronisation therapy (PPV-69.2%, NPV-75%; area under the ROC curve-AUC=0.736) (Figure 2B).

4. Discussion

An important observation that stems from the study is the fact that in response to resynchronisation therapy a significant role is played by the presence and degree of progress of chronic kidney disease (CKD) which commonly affects patients with heart failure, leading to the development of cardio-renal syndrome and the deterioration of the prognosis in these groups of patients. Noteworthy is the fact that, during the collection of data from the anamnesis, only 8 patients (17%) reported that they suffered from CKD (Table 1). Meanwhile, the results obtained clearly indicate that this problem affects a larger group of patients, and his understatement can result from a lack of awareness of the existence of the disease in the surveyed patients. It should be noted that all the patients presented reduced mean values of GFR-MDRD which permitted to determine the stage of CKD–in the group of responders-at stage 2, and in the group of non-responders-at stage 3 of CKD.

In the literature, we found much evidence of a role of initial GFR and creatinine in the evaluation of the response to CRT. The concentration of creatinine >1.2 mg/dl (which formed an element of the HF-CRT scale)is one of the factors of adverse prognosis in patients after the implantation of CRT-D [4]. It draws attention to the fact, that, as in our analysis, the mean concentrations of creatinine in the group of non-responders, throughout the entire period of observation, far exceeded this value and, at baseline, amounted to 1.36 mg/dl (120 µmol/l), while it is true that the initial value in the responders was close to 1.2 mg/dl (105 µmol/l=1.19 mg/dl), but during the 12-month follow-up it decreased. In addition, the cut-off point for creatinine, forecasting the positive response to CRT, was very close to that given in the HF-CRT scale and amounted to 1.14 mg/dl. Researchers from Pittsburgh, analysing the influence of kidney failure on the effect of CRT in 20-month observation, divided their patients into 3 groups, depending on the concentrations of creatinine-group 1-0.6-1.0 mg/dl, group 2-1.1-1.3 mg/dl and group 3-1.4-3.0 mg/dl. The highest observed rate of occurrence of the composite endpoint was detected in the group of patients with the baseline creatinine concentration >1.4 mg/dl, thus, concluding that the elevated value of creatinine before implantation of CRT-D is an independent predictor of total mortality, and also mortality and hospitalization due to HF [5]. Data from the literature provide the corresponding proposals for the output indications of GFR and point to the fact that GFR<60 ml/min/1.73

m^2 is an independent factor for increasing the total mortality and hospitalization due to HF [6, 7], and can also be associated with the lack of response to resynchronisation therapy defined by an improvement of echocardiographic parameters (decrease in LVESV by min. 15%) during a 6-month follow-up [8]. There are also individual reports, that, in the context of prediction of therapeutic response to CRT, estimate the cut-off point for the GFR value at <50 ml/min/1.73 m^2, and the conclusions remain the same as described above, i.e., patients with diagnosed CKD and GFR <50 ml/min/1.73 m^2 are characterized by a worse prognosis and are more likely to die from cardiovascular causes, and require hospitalization due to HF symptoms [9]. The examples mentioned above clearly attest to the influence of CKD upon the occurrence of mainly so-called hard endpoints, while the evaluation of function parameters can provide other conclusions. And so in one paper, which appeared in the last year, the authors acknowledged the increased mortality among patients with CKD and CRT-D, but they indicated that the clinical response to resynchronisation therapy, assessed inter alia on the basis of the NYHA classification and 6-MWT, was independent in terms of determining the characteristics of kidney failure before the procedure [10].

The issue of CKD in patients after CRT can also be considered in the context of the impact of this form of electrotherapy on improving renal parameters. Data from the literature on this subject does not provide definite conclusions. The results of our study document statistically significant differences in the GFR-MDRD values between the study groups in the 6^{th} month of observation (p=0.03), and the concentrations of creatinine (p=0.02) and GFR (p=0.01) in the 12^{th} month of follow-up. Among the responders to CRT, during the 12-month follow-up, we stated the improvement, but without statistical significance, in terms of the mean values of GFR by nearly 4.5 ml/min/1.73 m^2 in relation to the baseline values, while in the group of non-responders the mean GFR remained at similar level.

Authors from Cleveland carried out an analysis of 18 studies (14 observational and 4 randomized ones), on the basis of which they observed a slight improvement in renal function in patients with CKD and CRT-D, expressed as the increase in GFR by on average 2.3 ml/min/1.73 m^2 [11]. In the population of the MIRACLE study (NYHA III-IV, LVEF ≤ 35%, QRS>130 ms), in patients with resynchronising pacing, in comparison with a control group (CRT off), the researchers observed improvements in the GFR values by 2.7 ml/min/1.73 m^2 in the case of initially impaired renal function of a moderate degree (GFR <60 ml/min/1.73 m^2), what was not documented in patients with >GFR 60 ml/min/1.73 m^2 [12]. Similar observations were made by Adelstein et al. -not only they observed no improvement of renal function in patients with CRT-D and >GFR 60 ml/min/1.73 m^2, but also detected reduction in glomerular filtration rate in this group of patients. The group of patients in whom they found the improvement of GFR were individuals with severe renal failure, when GFR< 30 ml/min/1.73 m^2, but they achieved no benefit in terms of improved echocardiographic parameters (LVEF, LVESV) so as did the patients with less advanced CKD [13]. The Swiss investigators also noticed that the effect of CRT therapy upon the kidney function depended on the initial GFR value. Similarly, as in the previous study, they documented the improvement of GFR in patients in stage 4 of CKD, stable values (no improvement) in the case of GFR-30-59 ml/min/1.73m^2 and the decrease in GFR during the 2-year follow-up by about ml/min/1.73 m^2 in the group of patients in stage 1 and 2 of CKD [14]. Undoubtedly, due to the lack of coherent conclusions and observations from the studies conducted so far, the issue of interdependence between the

stage of CKD and the effectiveness of CRT requires further in-depth investigation.

5. Conclusions

Several important conclusions can be drawn from the analysis. Unquestionably, there was underlined the role of chronic kidney disease and its severity in assessing the response to cardiac resynchronisation therapy. Empirical cut-off points were determined for the initial concentrations of creatinine and GFR-MDRD, which could predict the positive therapeutic response to CRT. The effect of resynchronisation therapy on improving the kidney function remains debatable and requires further research. It draws attention to the fact that there exists unsizeable discrepancy between test results obtained in a laboratory that confirm the presence of CKD and low social awareness of the presence of the disease.

Acknowledgement of Grant Support

None declared

Conflicts of Interest

The authors report no relationships that could be construed as a conflict of interest

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Citation: Agnieszka Debska-Kozlowska, Marcin Ksiazczyk, Andrzej Lubinski. The Importance of Renal Function in Evaluating Response to Resynchronisation Therapy in Patients with Heart Failure after Implantation of Cardiac Resynchronisation Therapy and Defibrillator. Cardiology and Cardiovascular Medicine 3 (2019): 020-029.