Les résultats cliniques après la thérapie de resynchronisation cardiaque prédisent la survie chez les patients structurellement non répondeurs

Clinical outcome after cardiac resynchronization therapy predicts survival in structurally non-responder patients

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Résumé

Introduction : L'amélioration clinique était un critère d'évaluation principal dans la plupart des principaux essais cliniques qui ont façonné le paradigme de la thérapie de resynchronisation cardiaque, et quel que soit la réponse échographique (remodelage inverse), son impact sur la survie est peu étudié, en particulier dans le groupe de patients non répondeurs. Notre objectif est d'évaluer l'impact de l'amélioration clinique sur la survie des patients structurellement non répondeurs.

Méthodes et résultats : Nous avons analysé 152 patients ayant eu une implantation d'un pacemaker ou d'un défibrillateur triple-chambres dans le service de cardiologie du CHU de Sahloul Sousse.Après une durée de suivi variable, les patients ont été classés en fonction de leur réponse écho-cardiographique (les répondeurs ont été définis comme une augmentation de la FEVG > 5 % et/ou une diminution de la LVESV > 15 % par rapport à la valeur initiale).Par la suite, les non-répondeurs ont été analysés en fonction de leur amélioration clinique (définie comme une réduction significative et stable de la classe fonctionnelle NYHA >= 1).Enfin, 54 patients non répondeurs ont été identifiés et après un suivi moyen de 54 mois, 27 patients ont eu une amélioration significative de la classe fonctionnelle NYHA.Les résultats de survie étaient meilleurs chez les patients avec une amélioration clinique en analyse univariée (p = 0,025) et multivariée (HR = 0,51, IC [0,27 ; 0,96], p = 0,035).

Conclusion : Une amélioration clinique significative et durable chez les patients non répondeurs a démontré un fort impact sur la survie, ainsi, une réponse clinique peut être un prédicteur indépendant de la survie dans cette population.

Mots-clés

Thérapie de resynchronisation, Non répondeurs, Survie, Réponse clinique

Summary

Introduction: Clinical improvement was a primary endpoint in most of the major clinical trials that shaped the CRT paradigm, and regardless of left ventricle reverse remodeling its impact on survival is understudied studied particularly in non-responder patient group. Our aim is to assess the impact of clinical improvement on survival outcome of structurally non-responder patients.

Method and results: We analyzed 152 patients who underwent a successful CRT device implantation in the cardiology department of Sahloul University Hospital. After a variable duration of follow-up, patients were classified according to their echocardiographic response (Responders were defined as an increase in LVEF >5% and/or decrease of LVESV > 15% compared to baseline). Subsequently, non-responders were analyzed according to their clinical improvement (defined as a significant and stable reduction in NYHA class >= 1 class). Finally, 54 non-responder patients were identified and after a mean follow up of 54 months, 27 patients had a significant improvement in NYHA functional class. Survival outcome was better in patients with clinical improvement in univariate (p= 0.025) and multivariate analysis (HR=0.51, CI [0.27; 0.96], p= 0.035).

Conclusion: A significant and durable clinical improvement in non-responder patients has demonstrated a strong impact on survival, thereby, a clinical response may be an independent predictor of survival in this population.

Keywords

Cardiac resynchronisation therapie ; Non-responders; Survival; Clinical outcome.

Correspondance

INTRODUCTION

Since the early 00s, many randomized clinical trials (RCTs) had shaped and proved the efficacy of biventricular stimulation as a tool for cardiac resynchronization therapy (CRT). On this basis, CRT is now accepted as a standard non-pharmacological treatment of heart failure with reduced ejection fraction (HFrEF) (1).

Major studies (2,3) used improvements of left ventricle (LV) size and function as an important scale to predict a better long-term outcome for HFrEF patients undergoing CRT.

Therefore, patients who showed significant signs of left ventricle reverse remodeling (LVRR) were labeled as CRT responders. A cut-off of 15 % decrease in LV end-systolic volume (LVESV) is the most widely used echocardiographic parameter to define a favorable response (3,4).

Unfortunately, up to 30% of CRT recipients don't exhibit significant echocardiographic criteria of LVRR and consequently classified as non-responders (1). This population remains a fixed Achilles heel of CRT, offering great management challenges that require further investigation about the optimal scale to assess response and its possible determinants.

However, LVRR does not relate to clinical response according to some trials (5,6) and up to 63% of patients without LVESV improvement have a clinical response (6).

AIMS OF THE STUDY

We mainly aim through this work toassess the impact of clinical improvement on survival outcome of structurally non-responder patients.

PATIENTS AND METHODS

This is a single-center cohort study of patients who underwent a successful CRT device implantation in the cardiology department of Sahloul university hospital from 2006 to 2019.

Baseline clinical, electrical and echocardiographic data were gathered and analyzed retrospectively from the CRT patient registry.

A monitoring program has been set up to regularly follow patients and record clinical and echocardiographic parameters in outpatient clinics on the basis of a preprogramed scorecard.

Patients who died within one year after implantation as well as patients with a follow-up period less than 12 months were excluded from the study.

After a variable duration of follow-up and according to literature data (4, 7), we identified two response groups. Given the reliability of left ventricle ejection fraction (LVEF) and LVESV as parameters to identify CRT responders, patients in whom LVEF increased > 5% and/or LVESV decreased >15% compared to baseline were labeled CRT responders (as opposed to CRT non-responders).

According to major trials, the New York Heart Association (NYHA) functional class is a reliable parameter for predicting symptoms relief and less morbidity (7), therefore, a stable improvement of at least one class of NYHA is considered a significant clinical improvement in our study.

Our mainly end point is the death from all causes. Mid and long-term outcomes were subsequently analyzed.

STATISTICAL ANALYSIS

We used SPSS software to perform the appropriate statistical analysis. The quantitative variables were described according to the mean and standard deviation. Qualitative variables were described by frequency and percentage.

Comparisons of baseline characteristics and outcomes were performed using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the Student's t test for continuous variables.

Due to the longitudinal nature of the study, survival data analysis methods (Kaplan Meier) and Cox's regression model were used to meet the purpose of the study.

The origin would be the date of the CRT implantation, the event of interest would be death and the time period considered would be the duration of the last follow-up (the total duration of the follow-up, if applicable) or the duration of death, compared to the date of implantation.

RESULTS

1. Baseline patient characteristics:

We initially identified 169 patients eligible for the study, after excluding 10 patients who died within one year of implantation and 7 patients who have less than one year of follow up, a number of 152 patients were finally retained.

Only two patients had an epicardial LV lead placement following a failed coronary sinus catheterization. These

patients were excluded after their death within 12 months of implantation from septic complications.
During a mean follow up of 72 +/- 36 months, 54 patients (35.5%) failed to show an increase of > 5% in LVEF and/or > 15% reduction in LVESV, this population was identified as non-responders to CRT.
Baseline patient characteristics are shown in table 1. The mean age of our population is 57 +/- 12 years with male predominance (62%). The majority of patients have non-ischemic cardiomyopathy (74%) and are at NYHA class 3 (61%).
Most of the patients were in sinus rhythm (93%) with QRS duration > 150 ms (64%) and Left bundle branch block (LBBB) morphology (66.6%). Chronic renal failure was defined in our population by a creatinine clearance <60 mL / min.

2. Baseline characteristics of CRT non-responders according to their clinical improvement:

After a mean follow-up duration of 54 months, there were 27 patients (50%) with an improvement > 1 class of NYHA among the 54 non-responder patients.

Comparison of clinical, echocardiographic and procedural data between the two groups are shown in table 1 (with and without clinical improvement among CRT non-responders).

No differences found between the 2 groups in age, gender, baseline NYHA class, history of diabetes or hypertension (HTN), sinus rhythm, chronic kidney disease (CKD), ischemic cardiomyopathy proportion, prevalence of LBBB, QRS duration, left ventricular dimensions or systolic function, baseline mitral regurgitation (MR) or proportion of CRT with defibrillation (CRT-D) function during follow-up.

There were 18 patients died in non-responder group (33.3%), with non-significant difference in mortality between the two groups of clinical improvement (29.6% vs 37% p= 0.65).

3. Impact of clinical improvement on survival outcome of structurally non-responder patients.

For a better understanding of the survival prognosis in non-responder patients, we used clinical outcome

Table 1: Baseline characteristics of non-responder patients:

Baseline parameters	All patients (n= 152)	CRT non-responders (n= 54)	CRT non-responders with clinical improvement (n= 27)	CRT non-responders without clinical improvement (n= 27)	P value
Mean age (years) / SD	57 +/- 11	57.3 +/- 12	58 +/-10	56.5 +/- 14	0.67
Male gender n (%)	86 (57)	34 (62)	17 (63)	17 (63)	1
Ischemic cardiomyopathy n (%)	30 (20)	14 (26)	8 (29)	6 (22.2)	0.23
NYHA class III n (%)	100 (66)	33 (61.11)	23 (85.1)	10 (37)	0.01
Diabetes n (%)	47 (31)	12 (22.2)	7 (26)	5 (18.5)	0.57
HTN n (%)	60 (40)	14 (26)	7 (26)	6 (22)	0.79
CKD n (%)	55 (36.5)	21 (40.4)	7 (26)	14 (51.8)	0.55
Sinus rhythm n (%)	139 (91.4)	50 (93)	26 (96.2)	24 (90)	0.54
LBBB n (%)	117 (77)	36 (66.6)	22 (81.5)	14 (51.8)	0.18
QRS duration mean/ SD; (ms)	159 +/- 21	160 +/- 23	164 +/- 22	157 +/- 24	0.32
LVEDV mean/SD; (ml)	225 +/- 87	237 +/- 97	224 +/- 65	254 +/- 127	0.35
LVESV mean/SD; (ml)	171 +/- 76	181 +/- 95	169 +/- 74	206 +/- 136	0.44
LVEF mean/SD (%)	28 +/- 6	28.3 +/- 6.7	27.8 +/- 6	28.8 +/- 7	0.63
MR > grade 3 n (%)	15 (10)	5 (9.2)	1 (3.7)	4 (14.8)	0.44
CRT -D n (%)	32 (21)	11 (20)	3 (11.1)	8 (29)	0.23
Upgrading procedure n (%)	16 (10.6)	7 (12.9)	2 (7.4)	5 (18.5)	0.37
All causes of mortality n (%)	35 (23)	18 (33.3)	8 (29.6)	10 (37)	0.65

n: number, SD: standard deviation, HTN: hypertension, CKD: chronic kidney disease, LBBB: left bundle branch block, LVESV: left ventricle end systolic volume, ml: milliliters, LVEDV: left ventricle end diastolic volume, LVEF: left ventricle ejection fraction, MR: mitral regurgitation, CRT-D: cardiac resynchronization therapy with defibrillation function, ms: milliseconds.

defined as stable improvement of NYHA class, to determine whether it has an impact on survival of this population.

On univariate analysis using Kaplan Meier algorithms, survival in the subgroup of patients with significant clinical improvement is better than the subgroup without clinical improvement (P=0.025) (figure 1).

The 5 years survival probability is 82% for the subgroup with clinical improvement, while it is 73% for patient who didn't demonstrate significant clinical improvement.

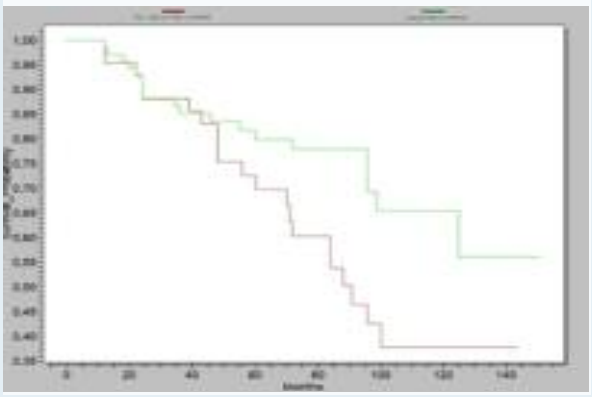

Figure 1: Kaplan Meier curves comparing survival based on clinical improvement of structurally non-responder patients

On multivariate analysis, we entered into a Cox proportional hazards model, variables that predict clinical outcome in these patients. When adjusting to ischemic cardiomyopathy, CKD, mitral regurgitation and LVEF subgroups, survival was significantly better in patients with clinical improvement compared to those without clinical improvement (HR 0.52 [0.27-0.96]; p=0.035) (Figure 2; Table 2)

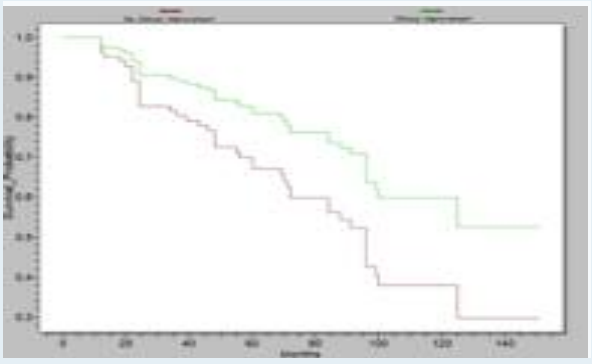

Figure 2: Cox regression model curves comparing survival based clinical improvement of non-responder patients

Table 2 : Cox multivariate regression analysis in non-responder subgroups according to clinical improvement

Variable	HR	Confidence interval (CI) 95%	P value
Clinical improvement/No clinical improvement	0.52 1.6	[0.27 – 0.96] [0.7 – 3.7]	0.035 0.20
Ischemic cardiomyopathy	1.03	[0.51 – 2.09]	0.92
CKD	1.29	[0.81 – 2.06]	0.27
	0.76	[0.10- 5.72]	0.79
MR			
LVEF groups (%) 1) < 20 2/1 2) 20-30 3/1 3) > 30	0.70	[0.09 – 5.3]	0.73

DISCUSSION

To our knowledge, this is the largest Tunisian study on long-term outcomes of CRT of a real world, nationwide population of patients undergoing CRT, in terms of patient numbers and length of follow-up.

This sub-studyfocused on the assessment of clinical response of structurally non-responderpatients after a variable follow-up duration as well as the impact of clinical improvement on their survival outcome.

The main finding is that a significant clinical improvement (a sustained increase in> 1 NYHA functional class) was observed in 50% of non-responder patients, which has a strong impact on the survival results of this population.

The two subgroups of CRT non-responders were clinically comparable and when performing the analysis, non-responders with clinical improvement have a significantly better survival prognosis in univariate (p=0.025) and multivariate analysis (HR 0.52 [0.27-0.96]; p=0.035).

The concept of response is well developed in the field of cancer and is increasingly being used in cardiology field (8). As a result, patients who showed significant signs of LVRR are labeled responders after a defined duration of follow-up (9) and have a significantly better survival outcome compared with non-responders.

The rational reasoning behind measuring response is to prove the efficacy of CRT in heart failure patients and to guide them for a more personalized therapy.

In RCTs, the effect of CRT is expressed in absolute and relative risk reduction in adverse clinical outcomes in relation to a control group (usually optimal medical therapy only) (10). While, in observational studies which based on systems/payers - doctors relationship, it results in a significant reduction in mortality, hospitalization

rates and a significant improvement in LV function in order to measure its costeffectiveness.
Whilst, RCTs measures are useful in daily practice to quantify the clinical effectiveness from patient-physician relationship perspective, they probably lack of meaning for the patient who wishes to know whether this device therapy has a positive impact on their long-term survival prognosis.
Numerous studies confirm that patients who demonstrate significant signs of LVRR have better outcomes especially in survival prognosis(4-7).
This survival gain in responders appears to arise from the occurrence and extent of LVRR and is highly related to improvements in left ventricular size and function. Hence, it has been suggested by many studies (5, 12-15) that a better survival outcome after CRT results from echocardiographic improvement rather than improvement in NYHA functional class.
Indeed, Bleeker et al.(16) demonstrated that the likelihood of improvement in NYHA class increased in parallel to the extent of LV reverse remodeling.
Nevertheless, according to Ypenburg et al.(6), LVRR does not relate to clinical response and up to 63% of people without LVESV reduction > 15% have clinical response.
The disparity between these two scales for assessing response in CRT patients -as demonstrated by numerous studies(5,6,17)- had been a trigger suggesting a possible impact of clinical improvement on survival.
Structurally non-responder patients place a heavy burden on both management systems and clinical management, which require a personalized approach for optimal therapy and a detailed measurement of CRT efficacy, therefore, studying the fate of non-responders beyond LV structure and function is mandatory.
Like most studies (12,15,17), we used a durable improvement of at least one NYHA functional class to define a significant clinical response. After a mean follow-up of 54 months, survival outcome of non-responder patients with clinical improvement was significantly better in univariate (p=0.025) and multivariate analysis (HR 0.52 [0.27-0.96]; p=0.035).
These results consolidate literature data about this subject, Kronborg et al (18), in 174 heart failure patient receiving CRT, clinical response to CRT was an independent predictor of mortality in the very long-term follow-up(HR: 3.02, 95% CI [1.71 - 5.38], P <0.001).

In Addition, Reitan et al (19), found that a self-assessed NYHA functional class two months after CRT was a strong predictor of long-term survival (HR: 0.59, 95% CI: [0.40-0.87], P <0.007).

To add emphasis about clinical response in non-structurally responder patients, Auger et al.(17), showed that as much as 28% of subjects with clinical improvement after CRT are not accompanied by significant echocardiographic response and are more likely to have ischemic cardiomyopathy.

Another prospective study of Rio et al.(15) investigated the benefit of LV size and function improvements on survival, showed that patients with LVRR had higher survival rates (80% vs. 64%, p=0.023) and fewer hospitalizations due to HF (11% vs. 48%, p<0.001), furthermore, among patients without LV improvements, 55% presented long-term improvement of ≥1 NYHA functional class and this was the strongest independent predictor of survival in these patients.
In fact, this clinical improvement despite the absence of reverse remodeling can be explained by a masked improvement in diastolic function due to a more synchronized biventricular depolarization, a more effective ventricular filling (with an adapted atrioventricular delay) and less mitral regurgitation.
Finally, this work is devoted to prove an impact of clinical improvement on survival outcome of this peculiar population. We have suggested that lasting improvement in NYHA functional class is an optimal scale for better understanding patient clinical outcomes (symptoms, quality of life, functional capacity, and hospitalization) and even for predicting mild and long-term survival outcome in structurally non-responder patients. Therefore, it is shown in this study that clinical improvement has a good impact on survival, hence it can be an independent predictor of better survival in the non-responder population.

Study limitations:
Data were collected retrospectively but follow up data were gathered prospectively. This was a single-center, non-randomized and non-controlled study, and this should be taken into consideration when interpreting the results.
Clinical response was based on improvement in NYHA class and did not include assessment of functional capacity or quality of life scores.
Follow-up duration was long enough to predict long-term outcomes but extremely variable between patients.
Survival analysis of non-responder subgroups was conducted with a relatively small number of patients.

CONCLUSION

Although, echocardiographic evidence of reverse remodeling is mandatory for a better survival outcome but for a better understanding of non-responder patient's outcome, this work is devoted to prove an impact of clinical improvement on survival outcome of this peculiar population. Indeed, a significant and durable clinical improvement in non-responder patients has demonstrated a great impact on survival, thereby, a clinical response may be an independent predictor of survival in non-responder population.

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