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Myocardial Scar Burden Independently Predicts Response to Cardiac Resynchronization Therapy

Shireen Shaban Mohammad, DRCPSC[1], Abdulmohsen Muhammed Almusaad, MD[1], Dalia Mohamed Ahmed MBBS, FRCPE [1], Alaa Eldin Rabea Abdelrheim, MD[2], Khaled Abdelghany Baraka, MD[2]

[1]King Abdulaziz cardiac center, king Abdulaziz medical city for national guard, Riyadh, Saudi Arabia
[2]Department of medicine, collage of medicine, Minya University, Minya, Egypt
***Corresponding author**:
Shireen Mohammad,
Shireen_ash@windowslive.com

ABSTRACT

Objectives: Cardiac resynchronization therapy (CRT) has been shown to improve quality of life and reduce mortality in patients with heart failure. Around 30 - 45% are non-responders to CRT. Determinants of response to CRT have been extensively studied. Faithful efforts were exerted to improve selection criteria for CRT beyond standard measures of electrical dyssynchrony. We aimed to assess the predictive value of amount and distribution of myocardial fibrosis to identify responders to CRT compared to conventional measures.

Methodology: 58 patients who underwent CRT implantation on the basis of standard indication were studied. All patients had available myocardial imaging (cardiac MRI or nuclear scan) prior to CRT. Images were analyzed for scar quantification and distribution. Multiple variables were studied. Receiver operator characteristic (ROC) curve analysis was used to evaluate the ability of Global scar to predict response to CRT.

Results: 30 patients of 58 were non-responders to CRT. 27 patients had non-ischemic cardiomyopathy, while 31 patients had ischemic cardiomyopathy. 19 patients (70.3%) in the non-ischemic group, and 9 patients (32.2%) in the ischemic group were responders to CRT, with a statistically significant difference, p- value: 0.002. A cutoff threshold of myocardial scar at 22.9% independently predicted response to CRT with a sensitivity of 70% and a specificity of 92.9%.

Conclusion: Global myocardial scar burden predicted response to CRT independent of etiology, regional distribution, and measures of electrical dyssynchrony

KEYWORDS: Cardiac resynchronization therapy, non-responders, myocardial scar, fibrosis distribution, electrical dyssynchrony, heart failure

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INTRODUCTION

Heart failure (HF) is a global complex clinical syndrome with a major morbidity and mortality burden. Worldwide, it is estimated that 56.2 million people are living with HF [1]. Around 1% to 3% of the overall population live with heart failure. In developed countries, the prevalence of HF is approximately 1%–2% of the adult population [2][3]. A heterogeneous group of etiological entities are implicated in the pathological process of cardiomyopathy and heart failure. Electromechanical dyssynchrony independently exacerbates heart failure morbidity and mortality [4]. Biventricular stimulation has been demonstrated to improve contractile performance in patients with mechanical dyssynchrony. Understanding of the electrophysiological, molecular, and mechanical mechanisms underlying reverse cardiac remodeling induced by CRT improved the selection of potential responders [4]. However, still 45% are non-responders to CRT [4].

Since CRT is a costly procedure and is not without hazard, it seems sensible to identify more precisely those who are candidates to get the best benefit and those who are unlikely to respond to CRT, but a precise definition of what constitutes a good or poor response is still controversial. Non-response to CRT has been extensively studied. Many solutions have been proposed, such as optimizing lead placement, creating automatic device algorithms to guarantee 100% biventricular pacing, and typical ECG criteria. However, non-response to CRT remains a challenging issue. Reasons for non-response to CRT may be multifactorial, partly due to an interplay between the site of pacing and the particular substrate being paced. Patients with ischemic cardiomyopathy, by definition, have fibrosis and scarring of ventricular myocardium. Patients with non-ischemic.

.cardiomyopathy also have significant burdens of ventricular scarring. Complex patterns of scar generate lines of conduction block and unpredictable patterns of wavefront propagation from LV pacing sites. Significant scar burden reduces the amount of viable myocardium amenable to CRT pacing, thereby diminishing response to CRT [5]–[7]. A strategy combining biventricular pacing and conduction system pacing has been suggested as a solution for non-responders with good outcomes [8]. Furthermore, feasibility of lead deployment and response to novel left bundle area pacing

(LBBAP) might be impacted by septal scar burden [9][10]. Therefore, an individualized approach to characterize myocardial substrate prior to CRT was proposed, particularly in patients presenting with non-LBBB morphology [11].

METHODOLOGY

This is a retrospective, single-center study. The study was approved by institutional review board of King Abdullah International Medical Research Center (KAIMRC). We screened who had been implanted CRT-D/P based on standard indication between (2013-2019) were enrolled. Patients remained in heart failure despite optimum medical therapy, New York Heart Association (NYHA) class II–IV, LVEF ≤35% due to ischemic or non-ischemic cardiomyopathy with evident electrical dyssynchrony indicated for CRT. Ischemic etiology was defined based on history of coronary artery disease, myocardial infarction or a performed coronary angiogram with obstructive coronary artery disease explaining severity of cardiomyopathy. Electrical desynchrony was defined by true LBBB based on Strauss criteria. QRS duration was automatically assessed from available ECGs. We included 58 patients who underwent cardiac MRI examination or nuclear scan within 3-6 months prior to CRT implantation and an echocardiogram within 6-12 months post procedure. Follow-up data was collected from available patient's records. Most of the patients underwent a standard LV lead position in lateral or posterolateral wall.

Scar Quantification:

An experienced cardiovascular imaging consultant blinded to the results analyzed cardiac MRI and nuclear images, assessed the extent and distribution of myocardial scar.

Cardiac MRI analysis:

For cardiac MRI images, scar size was quantified semi-automatically (General Electric, Discovery, MR450 1.5T). The short axis images were analyzed using a 17-segment model and commercially available software (Cvi42; Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Endocardial and epicardial borders were manually delineated. The scar percentage (total scar %) was automatically determined as a percentage of the myocardium using the full width at half maximum method (FWHM). Global myocardial scar was reported regionally as percentage of total. All scars were analyzed and reported the same way independent of underlying etiology. In order to assess whether regional variations in transmural scar percentage had an impact on CRT response, we divided the myocardium into four regions (septal, anterior, inferior, and lateral).

Nuclear scan images analysis:

Nuclear scan image analysis was performed using GE Healthcare, Chicago, Illinois, US. PET-CT, Discovery, powered 4DM software, maximization algorithm, a 17-segment model. Scar burden was calculated and expressed as a percentage of total number of myocardial segments with normal tracer uptake.

Definition of response:

Reverse remodeling is the primary end point for our study. Echocardiographic response was defined as ≥15% decrease in LV end-systolic volume (LVESV), and /or more than10% improvement in LVEF. Super-response was defined as an absolute improvement of LVEF to ≥50% for patients with baseline LVEF ≤35%. In addition, the percentage change in LVESV, LVEF, and LV end-diastolic volume (LVEDV) were measured 3months prior and 6-12 month after CRT implantation.

Regarding clinical data, information was collected from patients' records. We mainly relied on reverse remodeling measures in defining response rather than clinical response due to accuracy and availability of records of echocardiograms compared to less clear clinical data for some patients.

Statistical analysis:

Statistical analysis was performed using SPSS version 21. Continuous variables were analyzed using the independent sample t-test. Categorical variables were analyzed using the Fisher Exact test. Logistic regression analysis was used to study the associations. Receiver operator characteristic (ROC) curve analysis was used to evaluate the ability of Global scar to predict response to CRT. The optimum cutoff value was defined as the value that maximized the area under the ROC curve. For all tests, $P<0.05$ was regarded as statistically significant.

RESULTS

58 patients aged 22 to 77 years were included, 48 males (83%) and 10 females (17%). Mean age was not statistically different between responders and non-responders. 44% of males and 70% of females were responders to CRT, with non-significant difference, p-value: 0.1. Cardiac MRI was used for quantification of scar burden in 8 patients (13.79%). One patient (1.72%) was assessed using Technetium99, 35 patients (60.34%) were assessed with Rubidium82 and 14 patients (24.13%) using Fluorodeoxyglucose-positron-emission tomography (FDG-PET). There were no significant differences in QRS durations between responders and non-responders, either before or after CRT. Baseline LVESV before CRT was significantly larger in non-responders compared to responders p-value: 0.006. Likewise, LVESV after CRT was significantly larger in non-responders compared to responders p-value: 0.001. Baseline LVEDV before CRT was significantly larger in non-responders compared to responders p-value 0.002. LVEDV after CRT was significantly larger in non-responders compared to responders p-value 0.001as well. Global Scar burden was significantly extensive in non-responders compared to responders to CRT p-value: 0.001. Dependent-sample t-test showed insignificant change in QRS duration before and after CRT in responders and non-responders P-value: 0.018 and 0.337, respectively. A significant change in LVESV and LVEDV in responders compared to non-responders with P-value of 0.005 and 0.001, respectively. In view of the etiology, 27 patients had non-ischemic cardiomyopathy, while 31 patients had ischemic cardiomyopathy. 19 patients (70.3%) in the non-ischemic group, and 9 patients (32.2%) in the ischemic group were responders to CRT, with a statistically significant difference, p- value: 0.002. 15 patients were in Atrial fibrillation:

5 (33%) of them were responders to CRT. Five patients had a super response to CRT achieving significant improvement in LV systolic function >50%. The presence of significant mitral regurgitation (MR) was not statistically different between responders and non-responders. Dependent-sample t-test showing insignificant change in degree of mitral regurgitation before and after CRT in responders and non-responders, P-value: 0.083.

Figure and table legends:

Figure (1). Receiver Operating Curve: Area Under Curve (AUC) :0.856, cut off value of scar burden 22.9% with specificity of 92.9% and sensitivity of 70% - *P-value 0.001*

Figure (2). FDG-PET of a 48-year-old male CRT super-responder with non-ischemic cardiomyopathy in sinus rhythm with wide QRS duration (182ms). LVESV improved from 220 to 72mm3 with 0% scar burden, and LVEF improved from 25% to 50%.

Figure (3). FDG-PET of a 73-year-old male CRT non-responder with non-ischemic cardiomyopathy, sinus rhythm, no QRS shortening after CRT from baseline 156⇒156ms. LVEF: 25% before and after CRT. Global scar burden: 41.2% involving septal, anterior, apical, and lateral walls. The bottom right shows the cardiac MRI for the same patient showing LGE. The bottom left shows images using CVi42 software for scar quantification

Figure. (1)

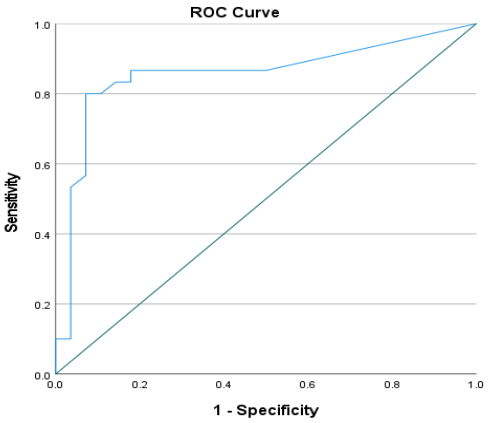

Figure. (2)

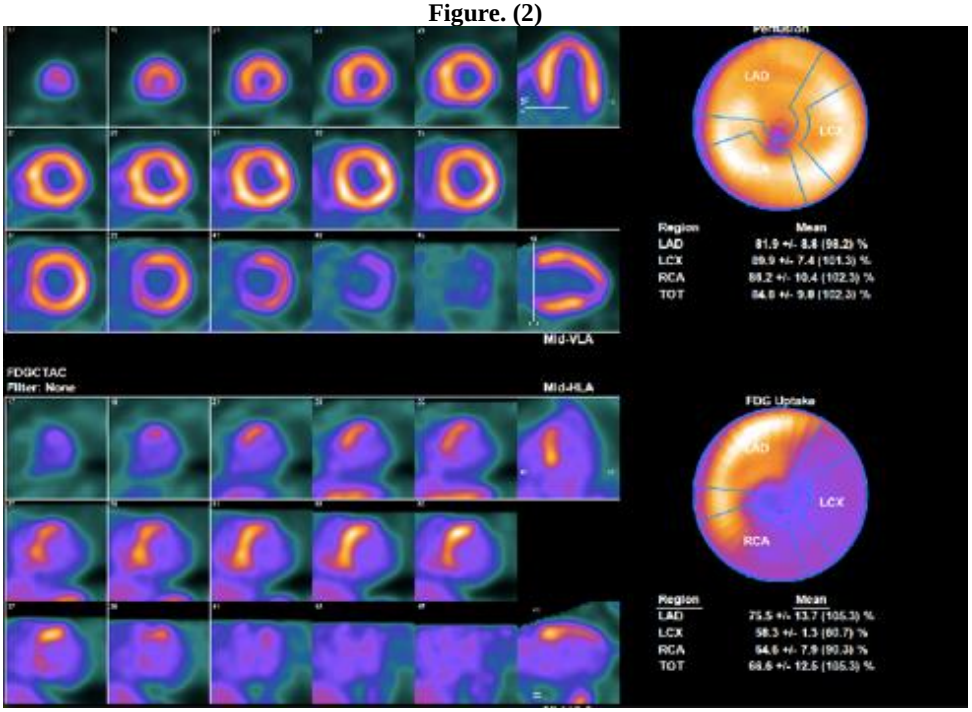

Figure. (3)

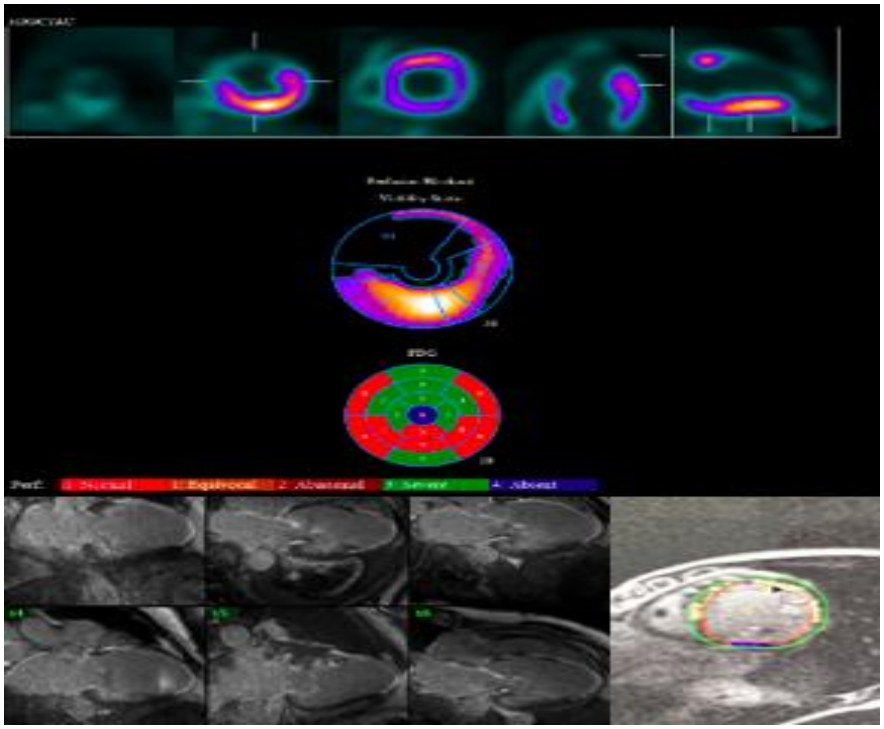

Table (1). Variables of CRT responders and non-responders

Variables	Responder, NO = 28	Non responder, NO = 30	p-value
Mean age at implantation (Years)	60.7±12.1	64.9±7.9	0.07
Male Female	21 (44%) 7 (70%)	27 (56%) 3 (30%)	0.1
QRS duration (msec) before CRT	159.5±19.1	153.2±23.4	0.3
QRS duration (msec) after CRT	149.6±21.9	148.4±22.1	0.8
LVESV, cm3 after CRT	66.1±36.3	159.1±64.7	0.001*
LVEDV, cm3 after CRT	124.3±48.8	223.6±69.7	0.001*
Left ventricular ejection fraction (LVEF) before CRT	24.87±3.588	24.14±4.596	0.6
LVEF, after CRT	45.96±5.011	25.34±3.254	0.001
Ischemic cardiomyopathy Non- ischemic cardiomyopathy	9 (32.1%) 19 (67.9%)	22 (73.3%) 8 (26.7%)	0.002*
Atrial fibrillation	5 (17.9%)	10 (33.3%)	0.2
Significant MR before CRT:	12 (42.9%)	19 (62.3%)	0.1
Significant MR after CRT:	6 (21.4%)	13 (43.3%)	0.1
Lateral wall Significant scar	0 (0%)	5 (16.7%)	0.5
Anterior wall: Significant scar	2 (7.1%)	19 (63.3%)	0.001*
Septal wall: Significant scar	2 (7.1%)	18 (60%)	0.001*
Inferoposterior wall Significant scar	3 (10.7%)	14 (46.7%)	0.004*
Global scar	4.7 ±10.4	29.9±17.5	0.001*

DISCUSSION

This is a retrospective single-center study from the Middle East, King Abdulaziz Cardiac Center, National Guard, Saudi Arabia. The main finding of our study is the great value of extent of myocardial scar burden to predict response to CRT. A cutoff threshold of myocardial scar at 22.9% independently predicted response to CRT with a sensitivity of 70% and a specificity of 92.9%. Multiple variables have been studied. Among them, total amount of myocardial scar, quantified by cardiac magnetic resonance (CMR) or nuclear imaging, showed great potential to identify non-responders. Interestingly, measures of electrical dyssynchrony such as QRS duration (QRSd) and LBBB morphology showed limited statistical power to identify non-responders. None of the specific scar regions (lateral, septal, anterior, inferior) were particularly associated with non-response to CRT, probably because most of our patients had extensive scars in multiple regions.

Our findings are in line with the outcome of several international studies. In 2019, Serge C. Harb et al. found that significant scar burden predicted response to CRT independently of LBBB morphology, QRSd, and LV lead tip location [12]. In a cohort of forty-five ischemic cardiomyopathy patients using global longitudinal strain, Antonello D'Andrea et al. revealed that extensive scar burden was an independent predictor of response to CRT [13]. Later on, the same authors reproduced those findings in a larger cohort of eighty-four patients. We found that most non-responders tend to be older (more than 75 years), male, and have ischemic cardiomyopathy. Consistent with our observations, Xu YZ et al. found that the extent of scar is significantly higher in non-responders, with a cutoff value of 22%. Furthermore, most of them had ischemic etiology and worse adverse remodeling at baseline. They were less likely to benefit from CRT [14].

We did not find an association between scar distribution and CRT outcome. Evan Adelstein and Samir Saba used Technetium-201 SPECT to assess the impact of scar on response to CRT in forty-nine patients with ischemic cardiomyopathy. They demonstrated that the presence of scar in close proximity to the site of LV lead inversely correlated with response to CRT. Total scar burden was an independent predictor of responders as well [15]. Association between distribution of scar and response to CRT has been a matter of controversy over the last two decades. David Birnie et al. found that responders to CRT had less lateral wall scar (5.6% compared to 24.5%) despite similar total and septal scar size in non-responders. They used Rubidium-82 and FDG-PET-CT to assess myocardial scar [16].

On the other hand, some authors believe that patients with ischemic cardiomyopathy should not receive CRT if they have significant non-viable myocardium, particularly in the septal and lateral walls [7]. In a multi-center trial, John M. Aalen et al. attempted to develop novel selection criteria to improve identification of responders to CRT. They assessed both myocardial work and viability (septum and lateral wall) using cardiac MRI. They proved for the first time their hypothesis that "Marked work asymmetry, reduced septal function in the presence of preserved viable septum, identified a contractile reserve which was activated by CRT." They confirmed the concept that there has to be enough viable myocardium to benefit from biventricular pacing [17].

Presence of scar tissue at the LV lead placement site was deeply evaluated in regard to benefit from CRT. Various imaging modalities and non-invasive mapping techniques such as ECGi were used to develop a comprehensive strategy to optimize lead placement. These studies highlighted the need for a personalized approach in selecting patients who are likely to benefit from CRT [18][19]. Patterns of electrical or mechanical activation, myocardial scar, and coronary venous anatomy were recommended to be considered in selecting the optimal target site for lead placement [18] [20].

Large studies such as STARTER and TARGET support avoiding LV lead placement within scar tissue whenever feasible. However, both large RCTs failed to show superiority of imaging-guided LV lead placement over the conventional electrical dyssynchrony method [19][20]. An explanation for the limited benefit of the imaging-guided approach is thought to be the inclusion of candidates with unsuitable coronary venous anatomy.

Singh et al. adopted a strategy using the longest electrical delay for Non-Left Bundle Branch Block Patients (ENHANCE-CRT study). They randomized 248 patients with non-LBBB to either a Q-LV-based or a conventional anatomical implantation approach. The results showed similar clinical outcomes and reverse remodeling for both approaches [21].

In a study of eighteen candidates for CRT, cardiac MRI imaging and coronary venous electroanatomic mapping were used to guide LV lead placement to the latest electrical activation area (remote from scar). The latest activated coronary vein was located within scar in 33% of the patients, which prevented optimal LV lead placement. This finding confirmed that the concept of late electrical activation should be used with care because scar tissue may show late activation [22].

In patients with LBBB morphology, there is considerable variation in the location of the latest activated region. Furthermore, defining the latest LV activation area is also dependent on variability of RV electrical and mechanical activation patterns [22]. Pacing scarred myocardium was associated with the worst outcomes, in terms of both pump failure and sudden cardiac death [23].
The "Does Electrical Targeted LV Lead Positioning Improve Outcome in Patients with Heart Failure and Prolonged QRS (DANISH-CRT) study" (NCT03280862) is an ongoing double-blind randomized controlled trial that will compare targeting the LV lead to the latest electrically activated area in a coronary venous tributary with conventional LV lead placement in an impressive large cohort of 1000 candidates for CRT with LBBB [24].

In a promising personalized CRT strategy, Tam TK et al. included twenty patients with non-LBBB (thirteen with right bundle branch block and seven with intraventricular conduction delay). CRT approach—either conventional Biv-Pacing or conduction

system pacing—was decided based on the shortest total activation time defined using intraoperative real-time 3D ECGi. This resulted in a higher rate (70%) of responders. The 3D-ECGi approach showed superior acute electrical resynchronization compared to the anatomical approach [7].

The utility of strategies assessing electrical activation pattern, scar burden, and coronary venous roadmaps goes beyond LV lead guidance in determining the optimum mode of resynchronization—especially in the modern era where conduction system pacing has evolved. For example, in cases of significant lateral scarring, conduction system pacing may be the favorable approach, while conventional Biv-Pacing may be more suitable in cases of septal scarring [25].

CONCLUSION

Despite enormous evidence of benefit of CRT from landmark clinical trials,[8,26] The problem of non-responders to CRT is still challenging. Candidates of CRT who have extensive myocardial scar, particularly ischemic cardiomyopathy, may not benefit from CRT. Prospective, larger studies are needed to confirm this result.

LIMITATION

The study design is retrospective analysis. We had a quite limited ability to precisely assess clinical outcome of some patients therefore; we mainly relied on measures of reverse remodeling to assess response to CRT. We were also limited by the number of included subjects who had available nuclear/ Cardiac MRI images amenable for analysis and scar quantification. Different imaging modalities were used to assess scar burden. We were not able to characterize myocardial tissue of LV pacing site.

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Conflict of interest

The authors declare that they have no conflict of interest

Foot notes:

Shireen Shaban Mohammad, DRCPSC
moved to Queen's university as cardiac electrophysiology fellow 2021
Present position: Senior registrar, cardiac electrophysiology, king Khaled hospital, Najran, Saudi Arabia
Dalia Mohamed Ahmed, MBBS, FRCPE
Present position: consultant cardiologist, multi-modality imaging, Hull University teaching hospital, United Kingdom

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