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Original Article

The role of early cardiac resynchronization therapy implantation in dilated cardiomyopathy patients with narrow QRS carrying lamin A/C mutation

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Abstract: Background: Dilated cardiomyopathy (DCM) caused by Lamin A/C gene (LMNA) mutation is complicated with atrioventricular conduction disturbances, malignant ventricular arrhythmias and progressive severe heart failure. Objective: We hypothesized that early cardiac resynchronization therapy (CRT) implantation in LMNA mutation carriers with an established indication for pacemaker or implantable cardioverter defibrillator (ICD), may preserve ejection fraction, and delay disease progression to end stage heart failure. Methods: We compared the primary outcomes: time to heart transplantation, death due to end stage heart failure or ventricular tachycardia (VT) ablation and secondary outcomes: change in left ventricular ejection fraction (EF) and ventricular arrhythmia burden between LMNA DCM patients in the early CRT and non-CRT groups. Results: Of ten LMNA DCM patients (age 51±10 years, QRS 96±14 msec, EF 55±7%) with indication for pacemaker or ICD implantation, five underwent early CRT-D implantation. After 7.2±4 years, three patients (60%) in the non-CRT group reached the primary outcome, compared to no patients in the CRT group (P=0.046). Four patients in non-CRT group (80%) experienced sustained ventricular tachycardia or received appropriate ICD shock compared to 1 patient (20%) in the CRT group (P=0.058). LMNA patients without early CRT had a higher burden of VPC/24 h in 12-lead holter (median 2352 vs 185, P=0.09). Echocardiography showed statistically lower LVEF in the non-CRT group compared to CRT group [(32±15)% vs (61±4)%, 95% CI: 32.97-61.03, P=0.016]. Conclusion: Early CRT implantation in LMNA cardiomyopathy patients, with an indication for pacemaker or ICD, may reduce heart failure deterioration and life-threatening heart failure complications.

Keywords: LMNA cardiomyopathy, cardiac resynchronization therapy

Introduction

Dilated cardiomyopathy (DCM) is defined as the presence of LV dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions [1]. Dilated cardiomyopathy (DCM) is a frequent reason for heart failure. Inherited forms of DCM are responsible for 50% of known cases [1]. Mutations in Lamin A/C gene (LMNA) appear as an increasingly diagnosed etiologic factor within the dilated cardiomyopathy disease spectrum [2]. Lamins A and C, encoded by the lamin A/C gene (LMNA), are major structural components supporting the inner nuclear membrane [3]. The cardiac phenotype of laminopathies is characterized by conduction disorder, atrial fibrillation, ventricular arrhythmias and dilated cardiomyopathy [4-6]. The incidence of life-threatening ventricular arrhythmia is high in patients with LMNA mutations and cardiac conduction disorders [7]. These arrhythmias, which cannot be prevented by a pacemaker occur in patients with LMNA mutation, cardiac conduction and preserved left ventricular function [7]. Implantable cardioverter defibrillator (ICD) implantation is considered for this patient population. Cardiac resynchronization therapy (CRT) improves symptoms and heart failure morbidity and mortality in patients with New York Heart Association functional class 3 or 4, left ventricular dysfunction and QRS prolongation [8-10]. CRT also pro-

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gressively improves left ventricular function, suggesting it might also delay disease progression in mildly symptomatic patients [11]. The results in the Resyncronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study confirmed that CRT induces reverse left ventricular remodeling and delays the time to first heart failure related hospitalization with further improvement over time [12]. In addition, it was demonstrated that some patients with heart failure and a narrow QRS complex may also exhibit left ventricular desynchrony and thus may benefit from CRT [13, 14]. From large scale pacing mode selection trials and observational studies, it has become apparent that a high amount of right ventricular apical pacing may be associated with a worse clinical outcome, deterioration of LV systolic function and development of heart failure [15-18]. These negative effects may be related to the induction of ventricular desynchrony by right ventricular apical pacing [18]. In a multicenter registry of LMNA mutation carriers, most patients who had a pacemaker at first contact were upgraded to CRT-D during the follow-up, apparently due to reduced ejection fraction [19]. Left ventricular dysfunction was the most crucial and inevitable manifestation associated with LMNA mutation that eventually leads to heart failure death [19]. At present, no data are available regarding the effects of early CRT-D implantation in LMNA mutation carriers with narrow QRS and relatively preserved ejection fraction who have an indication to pacemaker or implantable cardioverter defibrillator (ICD) implantation. We hypothesized that early CRT implantation in these LMNA mutation carriers may preserve ejection fraction and delay disease progression to end stage heart failure and death through left ventricular remodeling over a long-term follow-up.

Methods

Study population and genetic testing

This is an observational study performed at the Department of Cardiology at Rambam Health Care Campus (Haifa, Israel) during 2011-2019. Families with familial dilated cardiomyopathy were evaluated clinically and genetically in the Inherited Arrhythmia Clinic. In families with two or more affected members, blood samples were obtained after written informed consent then broad genetic testing targeting cardiomyopathy genes was performed in the proband. The genes were sequenced using xGen Exome panel v1.0 (IDT). All coding exons and flanking intronic regions were sequenced. Variants of interest were Sanger verified and classified for pathogenicity using the American College of Medical Genetics and Genomics guidelines [20]. Once a pathogenic or likely pathogenic LMNA mutation was identified adult first-degree relatives of the mutation carriers were offered mutation screening.

Inclusion criteria

Probands and relatives carrying the pathogenic or likely pathogenic LMNA mutation, who had an indication for device implantation, either pacemaker or ICD were included in the study.

Clinical work-up and outcomes

Probands and family members carrying a pathogenic or likely pathogenic LMNA mutation, who included in the study underwent a cardiac checkup every 6-12 months including a physical examination, electrocardiogram, exercise test, 12 lead 24-hour holter monitoring and a transthoracic echocardiography.

Our strategy was to implant CRT-D in LMNA mutation carriers who had an indication for device implantation, either pacemaker or ICD. All patients gave informed consent. The study was approved by the local IRB. This CRT group LMNA patients were compared to other family members who had already underwent device implantation (pacemaker or ICD) before the genetic diagnosis was established (non-CRT group).

The data was collected retrospectively and included baseline demographic (age, gender), electrogardiographic (ECG and 12-lead holter: heart rate, QRS duration, hemiblock) and echocardiographic characteristics (left ventricular ejection fraction (LVEF) and left ventricular end diastolic dimension (LVEDD). Atrial fibrillation, ventricular premature complex (VPC) burden, ventricular tachycardia, at the beginning, during and end of the follow up were recorded using ECG, exercise test and 12-lead holter. Left ventricular ejection fraction (LVEF) and left ventricular end diastolic dimension (LVEDD) at the beginning, during and end of the follow up were recorded using echocardiography.

The primary outcome was time to heart transplantation, death due to end stage heart failure and VT ablation. Other outcomes included change in LVEF, LVEDD, VPC burden and ventricular tachycardia during follow up. Primary and secondary outcomes were compared between CRT and non-CRT groups.

Statistical analysis

Continuous data were expressed as mean ± SD and compared with the 2 tailed Student t test for normally distributed parameters. Continuous non-normally distributed parameters were expressed as median and interquartile range (IQR) and compared by Mann Whitney test. For categorical variables data are expressed as number (percentage) and were compared using Fisher's exact/chi square test. The change in LVEF during the follow up was compared using repeated measure analysis model. Survival curve free of heart transplantation, death from end stage heart failure and VT ablation in LMNA patients with and without early CRT implantation were constructed using the Kaplan-Meier method and compared with log rank test. Two tailed $P \leq 0.05$ was considered statistically significant. The data were analyzed using SPSS software, version 28 (SPSS Inc, Chicago, Illinois).

Results

Baseline characteristics

During 2011-2019, 3/34 (8.8%) families with familial dilated cardiomyopathy (two or more family members affected) and likely pathogenic or pathogenic mutation in LMNA gene were identified. Seventeen patients (mean age: 50±14, 71% male) carried the causative LMNA variant. Seven patients, three asymptomatic and four who did not have indication for pacemaker or ICD implantation, were excluded from the analysis. Among the ten LMNA carriers who were included, five had a pacemaker or ICD implanted before the genetic diagnosis (non-CRT group). Five LMNA patients with novel indication for devise implantation (three for pacemaker and two for ICD) underwent CRT-D implantation (CRT group). The baseline characteristics of patients who met inclusion criteria stratified by CRT/no CRT, are presented in **Table 1**, as well as indications for device implantation for each group. All the patients in both groups had narrow QRS. There was no statistically significant difference in LVEF between groups at presentation (**Table 1**).

Follow up

During the follow-up of (7.2±4) years, 1 (20%) patient was transplanted, 1 (20%) died from end stage heart disease, and 3 (60%) necessitated VT ablation during the follow-up, all of them were from the non-CRT group. **Figure 1** shows the survival time to any of the primary outcomes of the patients in the CRT group and non-CRT group (P=0.046). Additionally, 4 (80%) patients in the non-CRT group experienced sustained ventricular tachycardia or received appropriate ICD shock as opposed to 1 patient (20%) in the CRT group who underwent appropriate ICD shock (P=0.058). **Table 2** shows electrocardiographic and echocardiographic characteristics at the end of the follow up. LMNA patients without CRT had a higher burden of VPC in 12 lead holter as compared to patients in the CRT group (median 2352/24 h, IQR 2185-2352 vs median 185/24 h, IQR 55-985, P=0.09). Echocardiography at the end of follow up showed statistically significant lower LVEF in the non-CRT group as compared to the CRT group [(32±15)% vs (61±4)%, 95% CI 32.97-61.03, P=0.016)]. **Figure 2** shows the LVEF at presentation and during follow up in patients carried LMNA mutation with and without early CRT implantation. Mean percentage of ventricular pacing was 98% in the CRT group and 80% in the non-CRT group. Two patients from the non-CRT group were upgraded to CRT at the end of follow-up when they had severely reduced LVEF. One of these patients died from end stage heart disease half a year after CRT implantation.

Discussion

This study presents the outcomes of predefined strategy of early CRT implantation in LMNA mutation carriers with either significant conduction disorder or ventricular tachycardia who had an indication for device implantation (pacemaker or ICD) regardless of EF or QRS duration. Our strategy proved to be effective in maintaining ejection fraction and preventing end stage heart disease during relatively long follow up in a small cohort. Life threatening heart failure complications as progression of heart failure,

Table 1. Baseline characteristics of the study population, at presentation, n=10

Variable	CRT (n=5)	No CRT (n=5)	p
Age at presentation, mean ± SD	53±12	50±5	P=0.6
Male sex, n (%)	4 (80%)	4 (80%)	P=1
PAF at presentation	4 (80%)	2 (40%)	P=0.5
Baseline ECG:			
HR, mean ± SD	42±12	45±15	P=0.8
LAHB, n (%)	2 (40%)	1 (20%)	P=0.4
QRS duration, mean ± SD, ms	92±16	100±12	P=0.8
Base line 12 lead holter:			
Min HR, mean ± SD	35±17	52±3	P=0.03
Max HR, mean ± SD	90±17	120±112	P=0.1
Mean HR, mean ± SD	55±4	72±6	P=0.01
VPC/hour, mean ± SD	100±90	499±478	P=0.2
Couple VPC	4 (80%)	1 (20%)	P=0.06
NSVT	2 (40%)	2 (40%)	P=1
Baseline echocardiograpy			
LVEDD, mean ± SD	5.3±0.3	5.5±0.2	P=0.4
LVEF (%), mean ± SD	61±2	48±12	P=0.09
CPK, mean ± SD, U/L	171±106	114±10	P=0.3
Medications, n (%)			
ACE inhibitors/ARB	5 (100%)	5 (100%)	P=1
Mineralocorticoid receptor antagonist	2 (40%)	3 (60%)	P=0.5
Indication for pacemaker			
Advanced AV block	3 (60%)	2 (40%)	P=0.5
Indication for ICD			
Sustained VT	1 (20%)	1 (20%)	P=1
Primary prevention, high risk	1 (20%)	2 (40%)	P=0.4

PAF, paroxysmal atrial fibrillation; ECG, electrocardiogram; HR, heart rate; LAHB, left anterior hemiblock; VPC, ventricular premature complex; NSVT, non sustained ventricular tachycardia; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; CPK, creatine phosphor kinase; ACE, angiotensin converting enzyme; ARB, angiotensin2 receptor blocker; AV, atrio ventricular; ICD, implantable cardioverter defibrillators; VT, ventricular tachycardia.

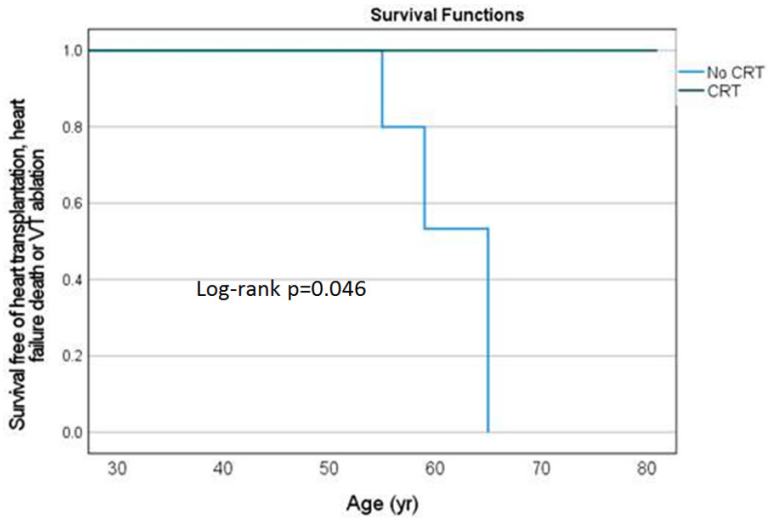

Figure 1. Kaplan-Meier estimate of the probability of survival free of heart transplantation, death due to heart failure and VT ablation in the CRT and non CRT groups.

death from end stage heart disease and VT ablation were prevented.

As far as we know early CRT implantation in LMNA cardiomyopathy has not been tested previously. Sidhu et al. retrospectively reviewed data from nine international centers and included LMNA mutation carriers who underwent CRT [21]. Sidhu et al. reported that CRT was implanted in 32 LMNA patients without class 1 or 2a indication. According to their report 23/32 patients improved or remained stable after CRT implantation [21]. Additionally, they reported that

Table 2. Electrocardiographic and echocardiographic characteristics at the end of the follow up, n=10

Variable	CRT (n=5)	No CRT (n=5)	p
PAF	3 (60%)	2 (40%)	P=0.5
NSVT per holter	4 (80%)	1 (20%)	P=0.06
Sustained VT	1 (20%)	2 (40%)	P=0.4
Number VPC/24 h, median, IQR	185, 55-985	2352, 2185-2352	P=0.09
VPC burden, percentage, median, IQR	0.3, 0.085-1.35	3, 2-3	P=0.09
LVEDD, mean ± SD	5.4±0.2	5.7±0.05	P=0.4
LVEF (%), mean ± SD	61±4	32±15	P=0.016

PAF, paroxysmal atrial fibrillation; NSVT, non sustained ventricular tachycardia; VPC, ventricular premature complex; IQR, interquartile range; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction.

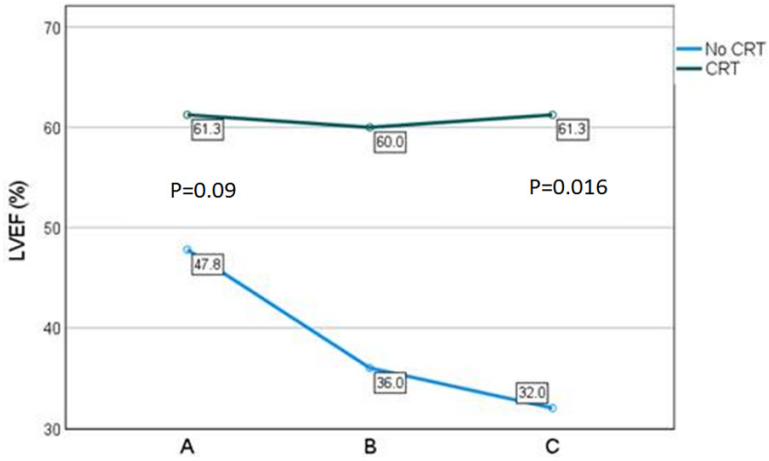

Figure 2. LVEF during the follow up in the CRT and no CRT group: A at presentation, B at the middle of the follow up and C at the end of the follow up.

65/105 LMNA patients who had CRT implantation were defined as non-responders. We hypothesized that this relatively high rate is due to non-early CRT implantation, as CRT was upgraded from pacemaker in 65% of patients and mean EF at the time of CRT implantation was approximately 33% [21]. As was shown in other studies left ventricular dysfunction is a late finding in LMNA heart disease and once present progress rapidly to end stage heart disease [22, 23]. This emphasizes the importance of early intervention to prevent left ventricular dysfunction.

The mechanism of progressive heart failure in LMNA cardiomyopathy is not well defined. Pacing induced desynchrony represents a potential contributor to disease progression and a remediable therapeutic target. An increase in the percentage of ventricular pacing pre-CRT in LMNA patients was significantly associated with CRT response [21]. Patients with cardiac implantable device, who had ventricular pacing ≥ 50%, were significantly more likely to have a CRT response than those with < 50% ventricular pacing [21]. Early CRT implantation and biventricular pacing instead of right ventricular pacing may prevent desynchrony and left ventricular deterioration in LMNA cardiomyopathy patients, regardless of EF and QRS duration.

Among the five patients in the non-CRT group in our cohort, three had indication for pacemaker (two for complete AV block and one for sick sinus syndrome) and two for ICD. One of the patients, who had an ICD for ventricular tachycardia, became pacemaker dependent during the follow up. Two of the five patients in the non-CRT group were not pacemaker dependent and didn't have high RV pacing burden. Thus, pacing induced desynchrony is most probably not the only mechanism that can explain progressive heart failure in these LMNA patients. The REVERSE study showed that CRT attenuated abnormal LV architecture, reduced LV size and improved LVEF by reverse LV remodeling with further improvement over time can delays the time to first heart failure related hospitalization [12, 24]. Prior studies have documented minimal occurrence of ventricular reverse remodeling with guideline directed medical therapy in this population [25]. We hypothesize that early CRT implantation may prevent left ventricular deterioration in LMNA cardiomyopathy patients by early reverse remodeling.

Conclusion

LMNA DCM one of the leading causes of heart failure, heart transplantation and sudden cardiac death. Our findings emphasize the value of early CRT implantation in LMNA cardiomyopathy patients who have an indication for pacemaker or ICD, in order to reduce heart failure deterioration and life-threatening heart failure complications. Larger studies examining the role of early CRT implantation in LMNA cardiomyopathy patients are needed.

Disclosure of conflict of interest

None.

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