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PhD THESIS

SUPER-RESPONDERS IN CARDIAC RESYNCHRONIZATION THERAPY WITH FUSION PACING

-ABSTRACT-

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INTRODUCTION

Heart failure represents a significant public health issue, leading to a reduced quality of life through disability and comorbidities. Since the treatment of heart failure varies depending on the etiology of the underlying cardiac dysfunction, it is imperative to define the pathology.

The past decades have brought significant contributions to the treatment of heart failure. However, pharmacological therapy maintained a high level of sudden cardiac death, thus the necessity for alternative treatment methods led to the widespread use of the implantable cardioverter-defibrillator. Subsequently, in the following years, a significant improvement in the prognosis of heart diseases was observed with the use of cardiac resynchronization therapy, which then became an essential part of treatment and one of the most important therapeutic advances in heart failure.

Despite significant progress, over 30% of patients do not respond to resynchronization therapy. Many methods have been studied in recent years to increase the response to therapy, however, even the most recent ESC guidelines do not recommend any specific strategy for programming resynchronization devices, with the vast majority remaining on nominal settings. Thus, the best method of optimization is still unknown and most research remains inconclusive. Traditionally, resynchronization therapy involves biventricular pacing, both right and left ventricular, being proposed as the conventional method. A few years ago, left ventricular-only pacing, known as "LV only pacing" with fusion, was proposed as an alternative to biventricular pacing. The results of studies allowed the inclusion of this option in the European Society of Cardiology guidelines for pacing and cardiac resynchronization therapy. This method is rarely used in clinical practice, although it is non-inferior to biventricular pacing.

GENERAL SECTION

HEART FAILURE AND CARDIAC RESYNCRONIZATION THERAPY

In developed countries, the age-adjusted incidence of heart failure appears to be decreasing, which might suggest better management of cardiovascular disease. However, due to aging, the incidence is increasing. In Europe, the prevalence was 17.20 cases per 1000 people per year, and the median incidence was 3.20 cases per 1000 people per year. There are significant variations in the burden of heart failure from a geographical and socio-demographic perspective.

Among specific causes, cardiomyopathy is a major factor. Sudden cardiac death, with an incidence of 0.15%-0.7% per year, continues to be a significant cause of mortality in cardiomyopathies. This underscores the importance of risk assessment.

Cardiac resynchronization therapy represents one of the most innovative advances in the treatment of heart failure. It was proposed in the 1990s as a new therapy for patients with a wide QRS complex and reduced ejection fraction despite medication treatment. Subsequently, the emergence of randomized studies led to its adoption in best practice guidelines in 2005, showing it to be an essential treatment. Over time, various pacing alternatives in resynchronization therapy have been proposed to increase patient response, from multiple pacing to endocavitary pacing.

Once activated, resynchronization therapy can reduce all three types of cardiac mechanical dyssynchrony. The previously dyssynchronous heart instantly benefits from coordinated contraction, thereby increasing cardiac output. In addition to the immediate hemodynamic benefits, which persist for several months, it improves both the anatomy and functionality of the heart. These long-term changes are known as reverse remodeling.

FUSION PACING

Fusion pacing stimulation is a programming strategy that maintains intrinsic atrioventricular conduction through the right bundle branch. Single-site left ventricular pacing can result in fusion of the intrinsic activation wave and the left ventricular pacing wave. Methods for optimizing fusion have emerged to simplify sophisticated echocardiographic optimization methods that were previously considered the gold standard.

However, fusion methods have potential limitations as they are typically performed at rest and in supine position. The impact of physiological factors such as physical activity, daily variations, posture, or vagal changes in heart rate frequency remains largely unknown. Moreover, it is unclear whether fusion is sufficient to account for these factors and significant variability among patients. There is currently no clear definition of patient characteristics that would benefit from fusion pacing beyond sinus rhythm, normal AV conduction, and left bundle branch block.

SUPER-RESPONDERS TO CARDIAC RESYNCRONIZATION THERAPY

Cardiac resynchronization therapy represents a cornerstone in the contemporary management of heart failure by reducing morbidity and mortality post-implantation in patients presenting with the triad: (1) symptomatic chronic heart failure, (2) ejection fraction ≤ 35%, and (3) wide QRS complex. However, the benefit for each patient can vary widely. While some patients demonstrate good or even excellent response (termed super-responders), others show poor or even absent response (Fig. 1).

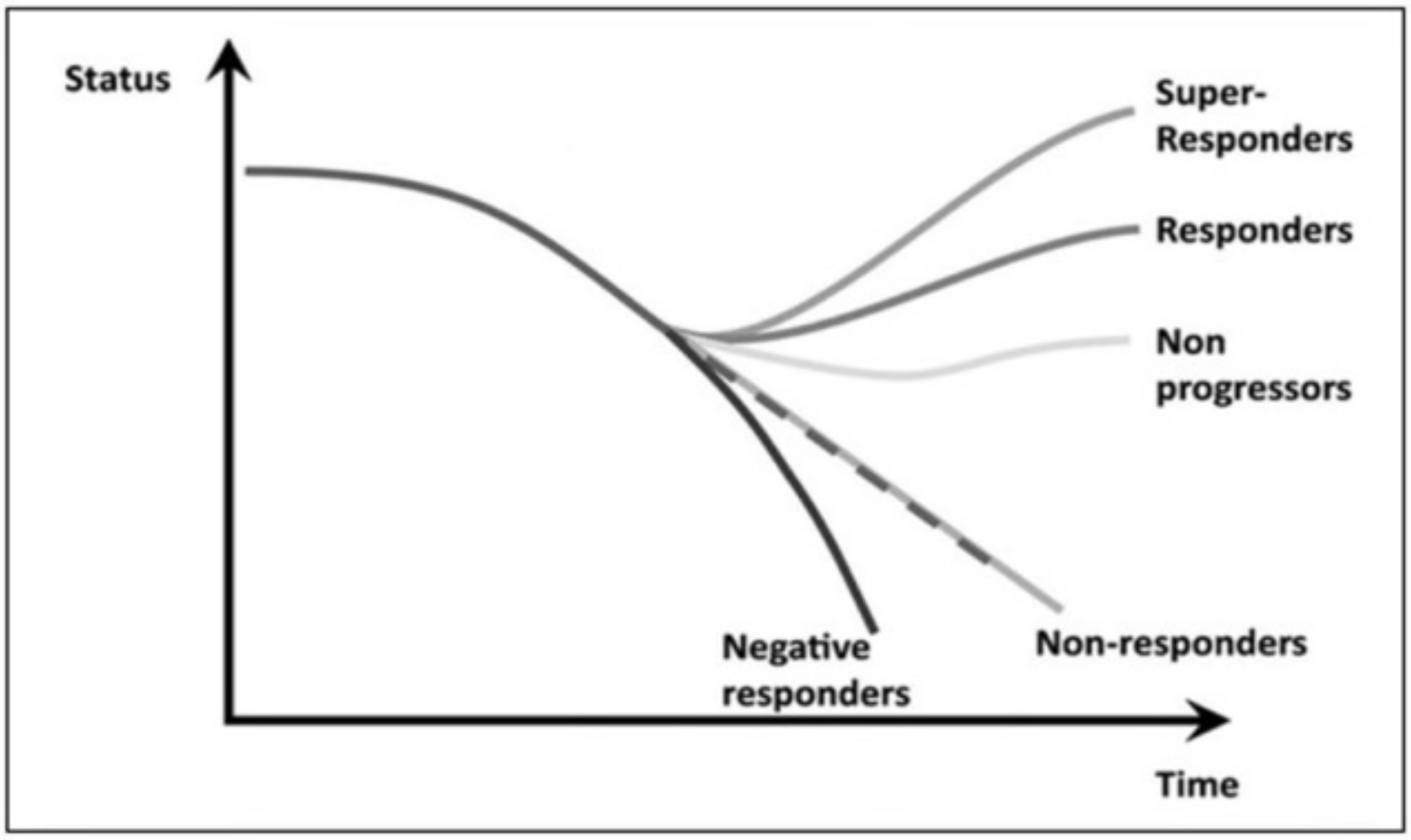

Figure 1. Possible response to cardiac resyncronization therapy over time

The objectives of resynchronization therapy aim to improve the number of super-responders among patients and optimize outcomes. With the help of technological advancements, some progress has been achieved. These include the ability to go beyond traditional methods of delivering resynchronization therapy, genetic testing to assess non-ischemic substrates, optimization of drug treatment, parameter pacing settings according to individual patient needs through echocardiography, exercise testing, and telemetric monitoring.

While the rate of non-responders has gradually decreased over the past 34 years of clinical use of resynchronization therapy, the rate of super-responders has remained stable over time, representing approximately 30% of all CRT patients, the latter being less studied. Currently, there are limited studies on a predictive model that can distinguish super-responders from eligible patients.

SPECIAL SECTION

Originality of the topic and the purpose of the study

Prediction of response to cardiac resynchronization therapy, especially super-response, is of great importance. Previously, identifying optimal predictors of response has gather significant attention. However, there is scarce data specifically on super-responders. Currently, the mechanisms by which some patients exhibit a profound response to resynchronization therapy while others have no benefit remain unclear, necessitating future studies to elucidate them.

Therefore, the aim of this thesis is to evaluate predictors for super-response to cardiac resynchronization therapy.

Study objectives

• Primary objective:

- 1. Identification of predictors for super-response to cardiac resynchronization therapy.

• Secondary objectives:

- 2. Evaluation of super-response in patients with normal atrioventricular conduction;
- 3. Genetic testing of a patient cohort and the contribution of these techniques to patient management;
- 4. Assessment of the efficiency of remote monitoring of patients with cardiac resynchronization devices.

The design and type of the study.

The present study was analytical, retrospective, and ultimately included 705 patients treated with resynchronization therapy. Patients were divided into

4 study groups according to the objectives of our study, and through their analysis, the results were published in 4 scientific articles, which constitute an integral part of this doctoral thesis.

The study description is depicted in the diagram shown in Figure 2.

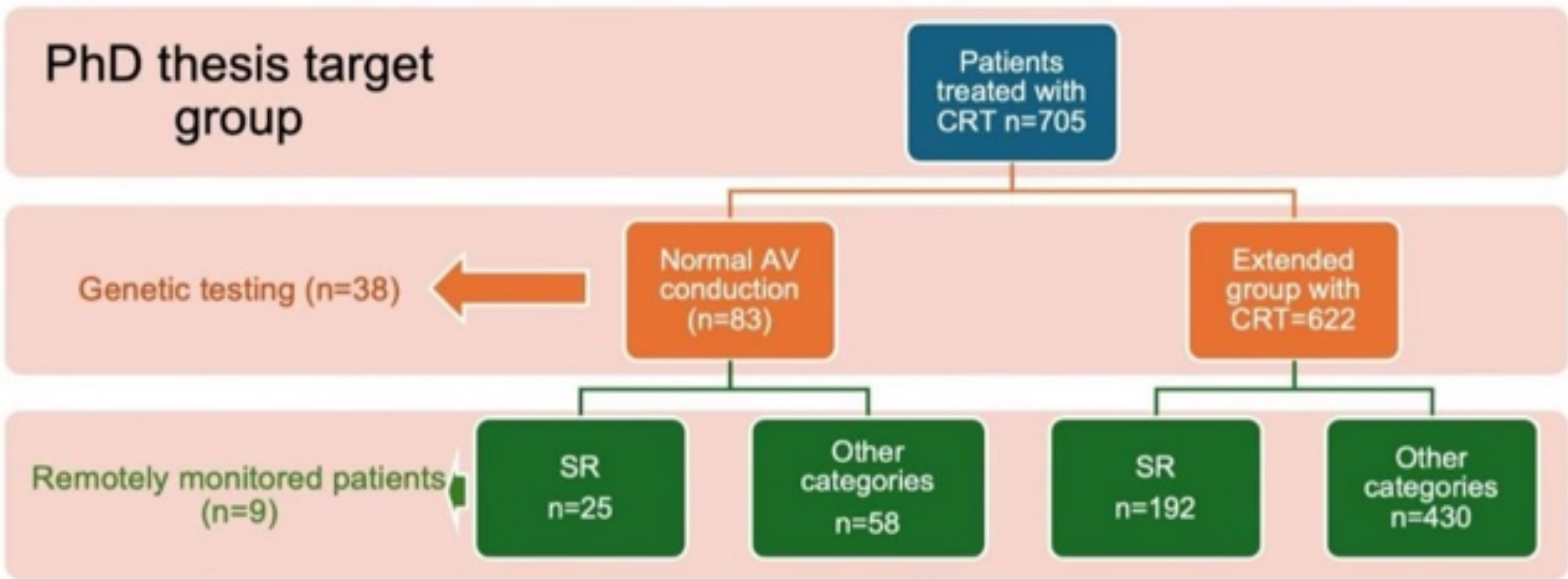

Figure 2. Design of the study.

In the analysis, 705 patients who underwent cardiac resynchronization therapy were included. Initially, we selected a cohort of 83 patients, among whom 25 were super-responders. Subsequently, we formed an extended group of patients who received resynchronization therapy, including those with normal atrioventricular conduction, altered atrioventricular conduction, or atrial fibrillation. Thus, we assembled a group of 622 patients, with 192 of them demonstrating a super-response to cardiac resynchronization therapy. Combining these two cohorts, we defined a third group of patients who underwent genetic testing panels for cardiomyopathies and arrhythmias. Finally, a group of only 9 patients receiving cardiac resynchronization therapy was remotely monitored, marking the first pilot study of its kind in our country. The main aim of the study, as initially stated, was to analyze predictors of super-response to cardiac resynchronization therapy, ultimately examining 217 patients who exhibited a super-response to this therapy.

Results

Nonischemic super-responders in fusion CRT pacing with normal atrioventricular conduction

Eighty-three patients were included, aged 62.3±9.2 years (60% male), with non-ischemic dilated cardiomyopathy, NYHA class II-III. All patients were implanted with an AD/VS pacing system between 2011 and 2021. All patients had a QRS complex >130 ms with typical left bundle branch block morphology.

There were no major intra- or peri-procedural complications during implantation. Initially, all devices were programmed at a resting rate of 50 beats/min and a maximum tracking rate of 130 beats/min. Individualized programming of the atrioventricular interval, with a stimulated atrioventricular interval of 148±21 ms and a sensed atrioventricular interval of 119±25 ms, enabled fusion pacing in all patients.

The average ejection fraction at baseline was 26.7±5.1%. All patients had severe left ventricular dilatation (mean LV end-diastolic volume 245.7±86.8 ml), significant left atrial dilatation (LA volume 101.9±33.1 ml), and pulmonary hypertension (PAPs 46.1±15.3 mmHg). Severe mitral regurgitation was found in 50% of patients initially, moderate in 40%, and mild in 10%.

The mean follow-up duration was 5 years ± 27 months (median 3.2 years, range 1 to 11 years). Thirty-one patients (40%) were implanted before 2016 and had more than 5 years of follow-up. The first patient implanted with a DDD AD/VS device has 10 years of follow-up and is a super-responder.

The study population was divided into two groups: super-responders (SR) and non-super-responders (responders and hypo-responders). Among the non-super-responders (69%), 52 were responders and 6 were considered hypo-responders at 6 months post-cardiac resynchronization therapy. Overall, our population had an extremely favorable outcome to fusion pacing, with more than a third being super-responders (31%). This could be explained by strict inclusion criteria (non-ischemic etiology, typical left bundle branch block, absence of severe comorbidities, and less severe NYHA II-III symptoms) in patients likely to have a long-term response.

No arrhythmic deaths were recorded in this population. Indeed, newer medications such as ARNI and SGLT2 inhibitors may influence outcomes in heart failure patients. However, this study analyzed the response to cardiac resynchronization therapy at 6 months of follow-up, with all patients on optimal medical treatment at implantation and during the 6-month follow-up period. Being on stable medication at baseline and at 6 months reduces the chances of potential interference with CRT response. Long-term follow-up will likely show that medication optimization plays a key role in maximizing CRT response. Medications such as beta-blockers and ivabradine were titrated based on exercise testing to maintain consistent fusion pacing long-term.

The conclusion of this study was that titration of beta-blockers/ivabradine and routine exercise testing during follow-ups for fusion pacing patients should be a standard approach to maximize resynchronization response.

Predictors for super-response in cardiac resyncronization therapy

The prediction of response to cardiac resynchronization therapy (CRT), especially super-response, is of great importance. The aim of this study was to evaluate predictors for super-responders to CRT.

A descriptive, retrospective study was conducted, including patients treated with CRT between January 2008 and May 2020. Patients with sinus rhythm and without significant atrioventricular conduction delay (PR <250 ms, Wenckebach point during atrial pacing <500 ms) were enrolled. We developed a personalized optimal fusion algorithm (OPT) primarily aimed at normalizing/improving left ventricular endocardial activation time using intracardiac interval and 12-lead ECG. The optimal fusion effect on synchrony and overall left ventricular function was clinically and echocardiographically evaluated at each standard follow-up visit (1 week, 1 month, 3 months, and later every 6 months) for CRT patients.

Initially, 797 patients were assessed for eligibility, but 175 were excluded for various reasons: lack of consent, lost to follow-up, death before the 6-month follow-up, permanent atrial fibrillation, and suboptimal left ventricular lead positions (e.g., anterior or anterolateral). Final analyzed data were obtained from 622 consecutive patients to avoid bias. The primary endpoint of our study was super-responder status defined as a left ventricular ejection fraction of at least 45% or an increase of at least 15%, and an improvement of at least two NYHA functional classes compared to the last follow-up level. Out of 622 patients, 192 were classified as super-responders.

The main findings of this study are as follows:

a) Left ventricular-only pacing with optimal fusion is an independent predictor for super-responders to CRT compared to conventional biventricular pacing.

b) In both the left ventricular-only pacing subgroup with fusion and the conventional biventricular pacing group, non-ischemic dilated cardiomyopathy was a predictive factor for super-responders to CRT.

c) QRS duration post-implantation is a predictor for super-responders only in patients with conventional biventricular pacing.

Remote monitoring in cardiac resynchronization therapy-first experience in Romania with a CRT virtual ward

Remote monitoring is becoming a standard of care for patients undergoing cardiac resynchronization therapy (CRT). This technology combines the use of cardiac pacemakers or implantable defibrillators with remote transmission to provide physicians with continuous, real-time information about the patient's heart activity. The aim of the study was to assess the feasibility and safety of remote monitoring technology in CRT follow-up patients.

Nine patients, aged 63.9 ± 10.4 years (78% male), with dilated cardiomyopathy in NYHA class II-III were included in the study. All patients received a resynchronization device (1 triple-chamber pacemaker and 8 triple-chamber defibrillators) with telemetry capabilities between 2021 and 2023. All patients exhibited a QRS complex >130 ms with typical left bundle branch block morphology.

The average follow-up period was 7.7 ± 4.8 months, with the longest follow-up being 18 months. Following device implantation with telemetry capabilities, patients were provided with remote monitoring devices. Immediately after the procedure, they were enrolled in a virtual clinic and trained by a physician on how to use the device at home. Regular virtual transmissions were scheduled automatically every 3 weeks under optimal transmission conditions (monitor plugged into power source, placed in the bedroom within 2-3 meters of the bed, transmissions occurring only at night during sleep with the patient present in the room at that time).

Major automated alerts were triggered for conditions such as fluid accumulation in the lungs (OptiVol alert), atrial tachyarrhythmias (atrial tachycardia/fibrillation), ventricular tachyarrhythmias, or device malfunctions. Patients also had the option to manually initiate transmissions based on symptoms (e.g., palpitations, dyspnea).

All patients adhered to the proposed protocol and accepted the telemetry device. During the follow-up period, 90 automated transmissions and 11 manual transmissions were collected and analyzed in the virtual hospital. Automated transmissions were successfully completed 94% of the time. Excluding transmissions related to the patient who was hospitalized due to severe pulmonary failure and subsequent mechanical ventilation following COVID infection, the success rate was 96%. Other reasons for transmission failures included monitor disconnection (1%), temporary absence from home (2%), or unstable GSM network connection (1%).

Out of a total of 101 transmissions to the virtual hospital, 11% were initiated manually by patients during symptomatic episodes. The majority of manual transmissions were due to episodes of atrial fibrillation (36%) or fluid accumulation (45%). Among those with atrial fibrillation episodes, half were newly diagnosed and required initiation of anticoagulant therapy. When signs of possible heart failure decompensation (OptiVol alert) were detected, outpatient diuretic doses were adjusted.

None of the patients requested discontinuation of monitoring or cessation of virtual transmissions. The study's outcome demonstrates that remote monitoring of resynchronization devices is not only feasible but also a safe approach for managing patients. Importantly, none of the patients experienced complications throughout the study duration.

A key conclusion of the study was that three patients (33%) were managed solely through telemetry means by the implanting physician. This suggests that remote monitoring can effectively replace in-person follow-up for a subgroup of patients, thereby reducing potential burdens on both patients and healthcare providers. Furthermore, treatment optimization was successfully achieved through telephone communication as needed, with no reported complications or adverse events.

Unexpected genetic twists in patients with cardiac devices

Genetic testing in patients with electronic cardiac devices shows promise for therapy optimization and improving outcomes. As our understanding of genetic substrates continues to expand, integrating genetic information into clinical decision-making processes will become increasingly crucial. By doing so, physicians can offer more personalized and effective treatments for patients with cardiac pacemakers, defibrillators, and resynchronization devices.

The study included thirty-eight patients, aged 44.5±13.1 years (58% male). All patients received an electronic cardiac device between 2018 and 2023. Nineteen patients (50%) had a family history of sudden cardiac death. Genetic testing focused on channelopathies and cardiomyopathies using commercially available panels ranging from 106 to 174 genes. Testing identified pathogenic (P) or likely pathogenic (LP) variants in 27 patients (71%), variants of uncertain significance (VUS) in 7 patients (18%), and negative results in 4 patients (11%).

Ten (26%) patients with dilated cardiomyopathy received cardiac resynchronization devices (7 triple-chamber defibrillators, 3 triple-chamber pacemakers). Patients were categorized into two groups: super-responders (SR) and non-super-responders (responders and hypo-responders). Super-responders were defined as those with stable left ventricular ejection fraction (LVEF) ≥45%.

All patients who received resynchronization devices and underwent genetic testing had non-ischemic cardiomyopathy. Among these, 70% received a triple-chamber defibrillator following cardiac arrest due to ventricular fibrillation or ventricular tachycardia (first cardiac event), while the remaining 30% received a triple-chamber pacemaker. One patient with a VUS-AGL mutation, potentially unrelated to underlying cardiac pathology, required an upgrade to a triple-chamber defibrillator due to recurrent ventricular tachycardia episodes, two years post-implantation. Additionally, the left ventricular lead was repositioned from an anterior to a lateral wall position intra-procedurally. Despite these interventions, this patient, like another with the same mutation (AGL), remained a non-responder. Another patient, despite meeting clinical and paraclinical criteria for super-responder status (non-ischemic, younger age, typical left bundle branch block, wide QRS, and posterior-lateral lead), died from refractory heart failure and electrical storm, having both TTN and TMEM43 mutations. Patients with multiple (polygenic) mutations tend to develop more severe disease and exhibit poorer response to cardiac resynchronization therapy. Moreover, despite being non-ischemic dilated cardiomyopathy, a patient with a TMEM43 mutation, known for extreme arrhythmogenicity, often has an unfavorable outcome, typically leading to exitus.

Considering our patient group, becoming a super-responder requires meeting both clinical and paraclinical criteria of a super-responder (non-ischemic etiology, younger age, typical left bundle branch block, wider QRS complex, and appropriate left ventricular lead position). Additionally, the absence of severe polygenic mutations is crucial.

Regarding mortality, 2 patients died during follow-up due to refractory heart failure, both with TTN (titin) mutation. A significant proportion of dilated cardiomyopathy cases are linked to genetic mutations, with titin mutation being the most common. Studies have shown that patients with this mutation have a worse prognosis, particularly higher incidence of heart failure progression and death, though the impact can vary based on individual patient factors. Early genetic screening and tailored therapeutic strategies are essential in managing dilated cardiomyopathy patients to improve outcomes and reduce mortality, including aggressive heart failure management and defibrillator use to prevent sudden cardiac death.

CONCLUSIONS

Pacing with fusion in cardiac resynchronization therapy shows a positive outcome in a group of patients with non-ischemic dilated cardiomyopathy and normal atrioventricular conduction, with over a third of patients being super-responders after 6 months of follow-up. Regular follow-ups (including exercise testing, echocardiography, device reprogramming, and treatment optimization) maximize the percentage of responders to cardiac resynchronization therapy.

Detailed analysis of predictors for super-responders across a much larger group of patients, including both ischemic and non-ischemic patients, revealed that left ventricular fusion-only pacing is an independent predictor for super-responders to CRT compared to conventional biventricular pacing. In both the left ventricular fusion subgroup and the conventional biventricular pacing group, non-ischemic dilated cardiomyopathy was a predictor for super-response to resynchronization therapy. Reduced QRS duration post-implantation is a predictor for super-responders only in patients with conventional biventricular pacing.

Regarding remote monitoring in patients with resynchronization therapy, we conducted the first study in our country evaluating the feasibility and safety of this monitoring mode. Findings indicate that telemetry is a viable and safe approach for managing resynchronization patients, offering promising solutions that provide comfort, cost savings, and efficient delivery of medical care.

Lastly, genetic testing has the potential to revolutionize decision-making processes for patients with cardiac electronic devices. By identifying genetic markers associated with arrhythmia susceptibility, etiology of heart failure, and response to cardiac resynchronization therapy, clinicians can tailor therapy to individual patient needs.