ORIGINAL ARTICLE

Incidence and Predictors of Ventricular Arrhythmia after Cardiac Resynchronization Therapy Device Implantation

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Background: Cardiac resynchronization therapy (CRT) serves as a pivotal therapeutic modality for patients with heart failure with reduced ejection fraction and biventricular dyssynchrony. The implementation of CRT not only mitigates the risk of sudden cardiac death but also enhances the overall quality of life. Knowledge concerning the incidence and predictive factors of ventricular arrhythmia (VA) following CRT implantation is invaluable for optimizing future CRT protocols and assessing cost-effectiveness.

Materials and Methods: The present research constituted a retrospective cohort analysis with a nested case-control study, conducted between January 2005 and April 2018. Inclusion criteria encompassed patients who experienced heart failure with a left ventricular ejection fraction (LVEF) of less than 35%, displayed a QRS complex duration exceeding 120 milliseconds on electrocardiography, which underwent optimized pharmacological treatment, and subjected to a minimum one-year follow-up post-implantation.

Results: One hundred forty-six CRT patients were included, and 47.9% (95% confidence interval [CI] 39.9 to 55.9) VA was detected. The average age at the time of implantation was 64 years. Only male, at 68.5%, was the baseline factor to increase the risk of VA (odds ratio [OR] 2.20, 95% CI 1.07 to 4.53, p=0.031). The other significant predictors for VA included fewer improvements in QRS width or LVEF post-implantation (p<0.001 and 0.001, respectively). Conversely, a reduction of at least 7 milliseconds in QRS width following implantation correlated with a significant decline in VA events (p<0.001), exhibiting a sensitivity of 80.3% and a specificity of 65.7%.

Conclusion: In patients who underwent CRT implantation, the risk factors determining the occurrence of VAs included male gender and minimal post-procedural improvements in QRS width or LVEF. On the contrary, a narrowing of the QRS width by more than 7 milliseconds post-implantation was significantly associated with a reduced incidence of ventricular arrhythmic events.

Keywords: Cardiac resynchronization therapy; Ventricular arrhythmia; Heart failure with reduced ejection fraction; Incidence; Predictors; QRS width

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Heart failure with reduced ejection fraction (HFrEF) stands as a significant risk for sudden cardiac death precipitated by ventricular arrhythmia (VA), even among patients optimized with pharmaceutical therapies[1]. Existing literature indicates that VA manifests in an estimated 40% to 60% of individuals diagnosed with HFrEF[2].

For patients with HFrEF, ventricular dyssynchrony is a prevalent issue. Cardiac resynchronization therapy (CRT) is advocated as a remedy to re-establish ventricular synchronicity. CRT is an intracardiac implantable electronic device (CIED) specifically indicated for heart failure patients characterized by a left ventricular ejection fraction (LVEF) below 35% and biventricular dyssynchrony, despite optimized medication[3,4]. Multiple studies corroborate that CRT implantation can improve quality of life, reduce heart failure hospitalization, and prevent sudden cardiac death[5,6].

CRT devices are divided into two categories, CRT with pacing functionality only (CRT-P) and CRT with an integrated defibrillator (CRT-D)[1,7]. The latter is indicated in instances of VA but carries an elevated risk of inappropriate electrical shocks, potentially resulting in psychological trauma, pulseless electrical activity (PEA), and cardiac arrest. Furthermore, in the Thai medical landscape, CRT-D devices are 1.5 to 2 times more costly than their CRT-P counterparts. The decision-making process for selecting between CRT-P and CRT-D becomes particularly challenging given that over 70% of CRT recipients exhibit

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positive responsiveness, culminating in enhanced cardiac performance that may obviate the need for a defibrillator[6].

Previous CRT-focused studies elucidate various variables that influence the efficacy of CRT[5,6,8-10] including gender, the underlying etiology of heart failure as ischemic versus non-ischemic, concomitant medical conditions such as hypertension, type 2 diabetes mellitus, dyslipidemia, and chronic kidney disease, presence of atrial fibrillation or flutter, prolonged QRS complex duration as electrical dyssynchrony[9], and LVEF from echocardiography[11]. It is posited that if CRT engendered substantial improvements in ventricular function, a concomitant reduction in VA incidence should be seen.

The present study aimed to investigate the incidence[12] of post-implantation VA and its correlated variables. With the identification of these predictive factors, the authors aimed to inform future decisions pertaining to the selection between CRT-P and CRT-D devices. Given the absence of existing research in this domain, the findings could contribute to cost-effectiveness in the context of Thai public health.

Materials and Methods

Study design

The present study was a retrospective cohort with nested case-control study by chart review conducted in a single center, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. Ethical approval for the present study was secured from the Institution's Ethics Committee. Data acquisition involved a retrospective chart review encompassing patient history, physical examinations, diagnostic evaluations, and CRT device interrogations conducted within the specialized pacemaker clinic. The primary objectives of the data collection were to ascertain the incidence of VA and to identify its predictive factors.

Study population

The present study population comprised all patients who underwent CRT implantation at the Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand, within the timeframe spanning between January 2005 and April 2018 and subsequently received follow-up care at the institution's specialized pacemaker clinic. Specific inclusion and exclusion criteria were rigorously applied as delineated below:

Inclusion criteria:

1. Patients were 18 years or older.
2. CRT implantations for either primary or secondary prophylactic indications must fulfill the following conditions:

2a. Demonstration of an LVEF of less than 35%, as ascertained via two-dimensional echocardiography conducted within one year preceding the CRT implantation, in conjunction with optimized pharmacological management.

2b. A baseline QRS complex duration exceeding 120 milliseconds as documented by standard 12-lead electrocardiography.

3. Post-implantation follow-up at Siriraj Hospital must extend for a minimum duration of one year.

Exclusion criteria:

1. Patients with a follow-up period of less than one-year post-implantation.
2. Individuals manifesting a QRS duration exceeding 120 milliseconds attributable to ventricular pacing prior to CRT implantation.

Study outcome

The primary outcome was the incidence of VA subsequent to CRT implantation. As defined by the American College of Cardiology Guidelines 2017 and the European Society Guidelines 2015, VA encompassed both ventricular tachycardia (VT) and ventricular fibrillation (VF)[13,14].

VT is characterized as a cardiac arrhythmia originating from the ventricles, manifested by a sequence of three or more consecutive complexes at a rate exceeding 100 bpm, with a cycle length of less than 600 milliseconds. It is further subclassified into non-sustained VT and sustained VT. Non-sustained VT refers to VT episodes that spontaneously resolve within a duration of less than 30 seconds, whereas sustained VT extends for a period exceeding 30 seconds or is accompanied by hemodynamic instability[13,14]. Conversely, VF is identified as a rapid, irregular ventricular rhythm with a rate exceeding 300 bpm or a cycle length of 180 milliseconds or less. It is distinguished by marked variability in QRS cycle length, morphology, and amplitude[13,14].

The secondary outcomes aimed to identify predictors of VA occurrence following CRT implantation. Specifically, the analysis would focus on examining the correlation between baseline patient characteristics, variations in QRS complex duration, and changes in LVEF pre- and post-implantation with the incidence of VA.

Statistical analysis

Based on prior published data[12], the estimated

incidence of VA was approximately 20%, utilizing a significance level (alpha) of 0.05 and a Z-score of 1.96. Consequently, the required sample size to evaluate the incidence of VA had been calculated to be 146 patients. To fulfill the sample size requirements for the study's secondary outcomes, a minimum of 42 patients within the VA group and 84 patients within the non-VA group would be necessary[9].

Descriptive statistical analyses would be employed to calculate both the incidence of VA and baseline characteristics prior to CRT implantation. As for the secondary outcomes, categorical variables would be analyzed using the chi-square test or Fisher's exact test as appropriated, while continuous variables would be analyzed via the Student's t-test or the Mann-Whitney U test, depending on the data distribution. The receiver operating characteristic (ROC) curve will be used to calculate the area under the ROC curve (AUC) for predicting the efficacy of change in QRS width by CRT and occurrence of VAs. The AUC that varies between 0.5 and 1.0, will represent the optimal cut-off value for determining the best accuracy. All statistical computations conducted using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval

The Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University (COA No. Si 146/2017) approved the study protocol.

Results

Patients' characteristics

During the study period extending between January 2005 and April 2018, a cohort of 146 patients who underwent CRT implantation was included, each with a minimum follow-up duration of one year. The baseline characteristics of the patients are shown in Table 1. Of the total implantations over the past thirteen years, 12 were CRT-P (8.2%), and 134 were CRT-D (91.8%). The average age at the time of implantation was 64 years, with an age range spanning from 22 to 89 years. The present study predominantly consisted of males, comprising 68.5% of the sample. The mean follow-up duration post-CRT implantation was 4.6 years, with a range of 1 to 13 years. All patients presented with a minimum New York Heart Association (NYHA) functional classification of Class II heart failure, and ischemic cardiomyopathy were diagnosed in 68 patients (46.6%). Comorbid conditions included type 2

Table 1. Baseline characteristics of patients

Baseline characteristics	Total n=146
Type; n (%)	
CRT-P	12 (8.2)
CRT-D	134 (91.8)
Sex; n (%)	
Male	100 (68.5)
Female	46 (31.5)
Age at implantation (year); mean±SD	64.2±12.8
• Range	22 to 89
BMI (kg/sqm); mean±SD (range)	24.3±3.7
• Range	15.6 to 32.9
NYHA; n (%)	
Class II	54 (37)
Class III	85 (58.2)
Class IV	7 (4.8)
Etiology of cardiomyopathy; n (%)	
Ischemia	68 (46.6)
Non-ischemia	78 (53.4)
Co-morbidity; n (%)	
Diabetes mellitus	60 (41.1)
Hypertension	95 (65.1)
Dyslipidemia	95 (65.1)
Chronic kidney disease	36 (24.7)
Stroke	11 (7.5)
Electrocardiography	
Rhythm; n (%)	
• Sinus	118 (80.8)
• Atrial fibrillation/flutter	28 (19.2)
Bundle branch block; n (%)	
• Left bundle branch block	101 (69.2)
• Non-left bundle branch block	45 (30.8)
QRS complex duration (ms); mean±SD	159.5±19.3
• Range	120 to 212
Echocardiography	
Left ventricular ejection fraction (%); mean±SD	25.4±6.2
• Range	10 to 35
Mitral regurgitation (degree); n (%)	
• None	50 (34.3)
• Mild	77 (52.7)
• Moderate	18 (12.3)
• Severe	1 (0.7)
Drug; n (%)	
ACEI/ARB	112 (76.7)
• Enalapril	52 (35.6)
• Losartan	29 (19.9)
• Candesartan	15 (10.3)
• Valsartan	8 (5.5)

CRT=cardiac resynchronization therapy; BMI=body mass index; NYHA=New York Heart Association; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; SD=standard deviation

Table 1. (continued)

Baseline characteristics	Total n=146
Drug; n (%)	
ACEI/ARB (continued)	112 (76.7)
• Captopril	3 (2.1)
• Irbesartan	2 (1.4)
• Lisinopril	1 (0.7)
• Perindopril	1 (0.7)
• Sacubitril/valsartan	1 (0.7)
Beta-blocker	129 (88.4)
• Carvedilol	110 (75.3)
• Bisoprolol	13 (8.9)
• Metoprolol tartrate	6 (4.1)
Mineralocorticoid receptor antagonist	86 (58.9)
Digoxin	62 (42.5)
Diuretic	121 (82.9)

CRT=cardiac resynchronization therapy; BMI=body mass index; NYHA=New York Heart Association; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; SD=standard deviation

diabetes mellitus in 41.1%, hypertension in 65.1%, dyslipidemia in 65.1%, chronic kidney disease in 24.7%, and stroke in 7.5%.

Baseline electrocardiography revealed 118 patients (80.8%) exhibited sinus rhythm, while the remaining 28 patients (19.2%) were diagnosed with atrial fibrillation or atrial flutter. The mean QRS complex duration was 159.5 milliseconds, ranging between 120 and 212 milliseconds. Left bundle branch block was observed in 101 patients (69.2%). Echocardiographic evaluations disclosed a mean LVEF of 25.4%, with a range from 10% to 35%. Functional mitral regurgitation (MR) was detected in 65.8% of the patients.

Incidence of ventricular arrhythmia after CRT implantation

Out of the 146 patients who underwent CRT implantation, VA manifested in 70 patients, representing an incidence rate of 47.9% with a 95% confidence interval (CI) of 39.9 to 55.9. Among the detected VA cases, non-sustained VT accounted for 50%, sustained VT for 37.1%, and VF for 12.9%. Patients presenting with sustained VT/VF necessitated therapeutic interventions, either in the form of ventricular overdrive pacing as anti-tachycardia pacing (ATP), or defibrillation, for arrhythmia termination. Conversely, patients with non-sustained VT did not require such interventions. The distribution of VA types is illustrated in Figure 1.

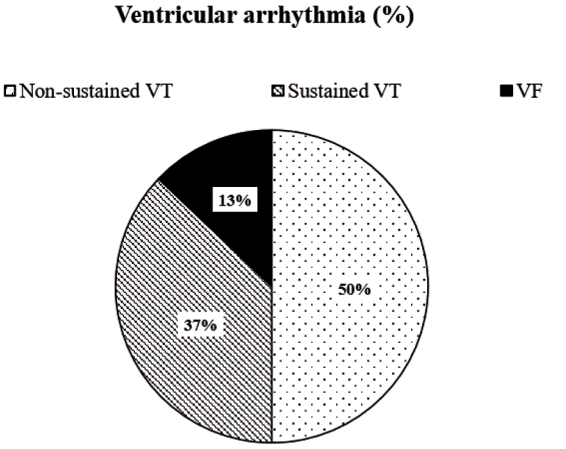

Figure 1. Types of ventricular arrhythmia post CRT implantation.
VT=ventricular tachycardia, VF=ventricular fibrillation

Predictors of ventricular arrhythmia

Among the baseline characteristics examined, only male gender was found to be statistically significant in increasing the incidence of VA, with an odds ratio (OR) of 2.20 (95% CI 1.07 to 4.53, p=0.031). No other baseline characteristics yielded statistical significance in relation to VA incidence. These associations between baseline characteristics and VA incidence are detailed in Table 2.

Two significant predictors were identified for a decrease in VA events post-CRT implantation, a greater narrowing of the QRS complex duration and improvement in left ventricular systolic function. Specifically, the study revealed statistical significance for these predictors with p-values of less than 0.001 and 0.001, respectively. Further details are shown in Table 3.

The ROC curve demonstrated that a reduction in QRS complex duration of at least 7 milliseconds offered optimal sensitivity and specificity as a predictor for VA. The associated metrics were as follows, sensitivity at 80.3%, specificity at 65.7%, positive predictive value (PPV) at 71.8%, and negative predictive value (NPV) at 75.4%. The overall accuracy of these predictive models was 73.3%. The AUC was calculated to be 0.737 (95% CI 0.653 to 0.822). The ROC curve is depicted in Figure 2.

Clinical improvement

Post-implantation clinical improvement as measured by the NYHA Classification was observed in 67.8% of the patients. Conversely, 32.2% of the patients exhibited either no improvement or

Table 2. Relationship between baseline characteristics and incidence of ventricular arrhythmia

Baseline characteristics	Ventricular arrhythmia		p-value
	Yes (n=70)	No (n=76)	
Sex; n (%)			0.031
Male	54 (77.1)	46 (60.5)	
Female	16 (22.9)	30 (39.5)	
OR 2.20 (95% CI 1.07 to 4.53)			
NYHA; n (%)			0.651
Class II	26 (37.1)	28 (36.8)	
Class III	39 (55.7)	46 (60.5)	
Class IV	5 (7.1)	2 (2.6)	
Etiology of cardiomyopathy; n (%)			0.144
Ischemia	37 (52.9)	31 (40.8)	
Non-ischemia	33 (47.1)	45 (59.2)	
Co-morbidity; n (%)			
Diabetes mellitus (n=60)	24 (34.3)	36 (47.4)	0.108
Hypertension (n=95)	49 (70.0)	46 (60.5)	0.230
Dyslipidemia (n=95)	48 (68.6)	47 (61.8)	0.394
Chronic kidney disease (n=36)	19 (27.1)	17 (22.4)	0.504
Stroke (n=11)	5 (7.1)	6 (7.9)	0.863
Electrocardiography			
Rhythm; n (%)			0.809
• Sinus (n=118)	56 (80.0)	62 (81.6)	
• Atrial fibrillation/flutter (n=28)	14 (20.0)	14 (18.4)	
Bundle branch block; n (%)			0.219
• Left bundle branch block (n=101)	45 (64.3)	56 (73.7)	
• Non-left bundle branch block (n=45)	25 (35.7)	20 (26.3)	
QRS complex duration (ms); mean±SD	156.6±22.3	162.0±15.7	0.090
Echocardiography			
Left ventricular ejection fraction (%); mean±SD	25.3±5.5	25.6±6.9	0.752

NYHA=New York Heart Association; OR=odds ratio; CI=confidence interval; SD=standard deviation

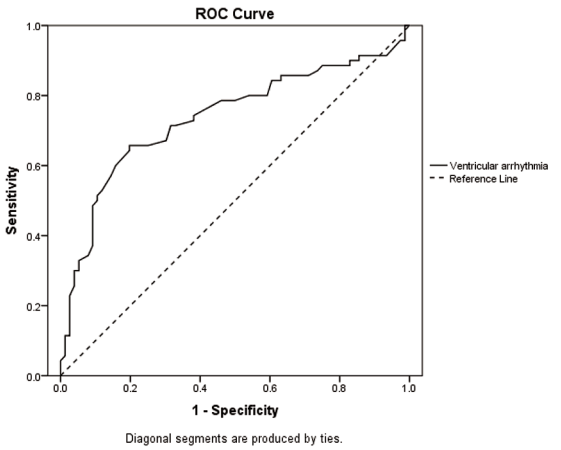

Figure 2. The ROC curve of change in QRS width at least 7 milliseconds and occurrence of ventricular arrhythmia (AUC 0.737, 95% confidence interval 0.653 to 0.822).

ROC=receiver operating characteristic, AUC=area under the ROC curve

clinical deterioration. Statistical analysis revealed no significant correlation between post-CRT clinical improvement and the incidence of VA (p=0.382).

Ventricular arrhythmia subgroup

Out of 70 patients diagnosed with VA, the classifications were as follows, 35 with non-sustained VT (50%), 26 with sustained VT (37.1%), and nine with VF (12.9%). The incidence of VA necessitating therapeutic intervention was 24.0% (95% CI 17.5 to 31.9). The relationship between baseline clinical characteristics and the incidence of sustained VT/VF post-CRT implantation is delineated in Table 4. Patients presenting with a baseline left bundle branch block exhibited a significantly reduced risk for the incidence of sustained VT/VF (OR 0.53, 95% CI 0.30 to 0.93, p=0.029). Moreover, a widening of the baseline QRS complex duration was also associated

Table 3. Relationship between electrical dyssynchrony, LVEF difference, and ventricular arrhythmia

	Ventricular arrhythmia		p-value
	Yes	No	
ΔQRS width (QRSpre CRT – post CRT, electrical dyssynchrony) (ms); mean±SD	0.9±29.2 (n=70)	22.7±21.2 (n=76)	<0.001
LVEF improvement (LVEFpost CRT – pre CRT) (%); mean±SD	5.4±10.4 (n=48)	13.2±12.9 (n=55)	0.001

LVEF=left ventricular ejection fraction; CRT=cardiac resynchronization therapy; SD=standard deviation

Table 4. Ventricular arrhythmia subgroup showing the relationship between baseline characteristics and incidence of sustained VT/VF

Baseline characteristics	Sustained VT/VF		p-value
	Yes (n=35)	No (n=111)	
Sex; n (%)			0.206
Male	27 (77.1)	73 (65.8)	
Female	8 (22.9)	38 (34.2)	
NYHA; n (%)			0.662
Class II	11 (31.4)	43 (38.7)	
Class III	23 (65.7)	62 (55.9)	
Class IV	1 (2.9)	6 (5.4)	
Etiology of cardiomyopathy; n (%)			0.068
Ischemia	21 (60.0)	47 (42.3)	
Non-ischemia	14 (40.0)	64 (57.7)	
Co-morbidity; n (%)			
Diabetes mellitus (n=60)	12 (34.3)	48 (43.2)	0.348
Hypertension (n=95)	25 (71.4)	70 (63.1)	0.365
Dyslipidemia (n=95)	23 (65.7)	72 (64.9)	0.927
Chronic kidney disease (n=36)	10 (28.6)	26 (23.4)	0.538
Stroke (n=11)	5 (14.3)	6 (5.4)	0.084
Electrocardiography			
Rhythm; n (%)			0.260
• Sinus (n=118)	26 (74.3)	92 (82.9)	
• Atrial fibrillation/flutter (n=28)	9 (25.7)	19 (17.1)	
Bundle branch block; n (%)			0.029
• Left bundle branch block (n=101)	19 (54.3)	82 (73.9)	
• Non-left bundle branch block (n=45)	16 (45.7)	29 (26.1)	
QRS complex duration (ms); mean±SD	150.6±21.6	162.2±17.7	0.006
Echocardiography			
Left ventricular ejection fraction (%); mean±SD	24.9±5.4	25.6±6.5	0.537

VT=ventricular tachycardia; VF=ventricular fibrillation; NYHA=New York Heart Association; SD=standard deviation

Table 5. Relationship between electrical dyssynchrony, LVEF difference and sustained VT/VF

	Sustained VT/VF		p-value
	Yes	No	
ΔQRS width (QRSpre CRT – post CRT, electrical dyssynchrony) (ms); mean±SD	–8.74±29.3 (n=35)	18.86±23.4 (n=111)	<0.001
LVEF improvement (LVEFpost CRT – pre CRT) (%); mean±SD	4.92±10.6 (n=23)	10.6±12.6 (n=80)	0.027

LVEF=left ventricular ejection fraction, CRT=cardiac resynchronization therapy, VT=ventricular tachycardia, VF=ventricular fibrillation

with a significantly decreased risk of sustained VT/VF (p=0.006).

Similar to the factors influencing the overall incidence of VA, a greater reduction in QRS width and an improvement in LVEF were found to significantly decrease the incidence of sustained VT/VF. These associations are quantitatively delineated in Table 5.

Discussion

The present study, which collected data between January 2006 and April 2018, included a cohort of 146 patients. The observed incidence of VA in the present single-center study was 47.9%, similarly with the previous rates of 40% to 60% among patients with HFrEF undergoing optimal medication therapy alone[2].

In terms of baseline characteristics, male gender was the only factor that significantly increased the incidence of VA, corroborating the findings of García-Lunar et al[12]. Contrarily, females were identified as good responders to CRT, exhibiting reduced VA post-implantation. When comparing non-ischemic to ischemic cardiomyopathy patients, no significant difference was found in the rates of ventricular arrhythmic events requiring therapeutic intervention (p=0.144). This is in line with the previous research by Karaca et al[9]. Furthermore, more improvements in QRS width and LVEF following CRT implantation were associated with a decrease in VA events. In the study of García-Lunar et al.[12], persistent electrical dyssynchrony associated with four times increasing of VA at 38% versus 9%. Similar to the previous study of Manfredi et al.[15], the study demonstrated that near normalization in LVEF higher than 45%, the incidence of implantable cardioverter defibrillator (ICD) therapy for VAs becomes low. All these analyses implied that, for the next pulse generator change, if the female patient was a good CRT responder[9,10,12,15] with an improvement of QRS width or LVEF, CRT-D might not be required.

The present study subgroup analysis of sustained VT/VF revealed that 24% of these instances required therapeutic intervention. More improvements in QRS width and LVEF after CRT implantation significantly reduced the incidence of sustained VT/VF events, while gender did not correlate with such events. Interestingly, longer baseline QRS durations were found to decrease the risk of sustained VT/VF post-implantation, indicating a need for further studies with larger sample sizes to validate this observation.

The present study has limitations, including its retrospective cohort design with a nested case-control study, its single-center focus, and the small size of the study population, which may contribute to incomplete data collection. To establish expanded best practices regarding CRT-P versus CRT-D implantation, multi-center randomized studies will be essential for better understanding the impact on VA incidence and overall mortality benefits in HFrEF patients.

Conclusion

In the authors' single-center study, the implantation incidence of VA was found in nearly half, of which 53.4% were identified as non-ischemic cardiomyopathy. The post-implantation data revealed that a greater narrowing of the QRS width or an improvement in LVEF was significantly correlated with a reduced risk of VAs. For these patients, CRT-P should be considered during future pulse generator replacements to reduce cyclic trauma from inappropriate defibrillator shock and save the patient's expense.

What is already known on this topic?

Incidence and predictors of VA after CRT device implantation.

What does this study add?

Guidance for choosing the patient for CRT-P or CRT-D.

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Conflicts of interest

The authors declare no conflict of interest.

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