Original Article

Evaluating the efficacy, safety, and predictors of failure following cardiac resynchronization therapy in a developing country: an ambispective, multi-center study

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Background: Multiple studies have demonstrated that cardiac resynchronization therapy (CRT) effectively improves the prognosis of heart failure. CRT has been proven to improve patients' quality of life and reduce the risk of readmission and death in selected patients. Nevertheless, a notable proportion of individuals undergoing CRT showed no response. Therefore, we conducted this study to describe CRT characteristics and reported the outcomes 1 year after discharge in Vietnam, along with predictors of non-response to CRT.

Methods: This was a multicenter, ambispective cohort study that enrolled all CRT implantation patients at five hospitals in Ho Chi Minh City: University Medical Center Ho Chi Minh City, Heart Institute of Ho Chi Minh City, Tam Duc Heart Hospital, Thong Nhat Hospital, and Vinmec Central Park Hospital. All patients received treatment according to established guidelines and were monitored for up to 1 year after being discharged. Primary outcomes included rehospitalization and mortality rate 1 year after discharge. Secondary outcomes included early and late complications related to the procedure.

Results: Between April 2016 and April 2020, 88 cases of successful CRT implantation from five hospitals were enrolled. The majority of the population was male (68.2%), mean age was 62.5±13.4 years old, New York Heart Association (NYHA) III/IV at admission (98.9%), and the mean left ventricular ejection fraction (LVEF) was 24%±5.9%. The incidence of early complications was 9.1%. The overall mortality rate was 12.5%, with 6.8% occurring within the 1-year follow-up period. The population experienced a significant decrease in readmission rate within 1 year after discharge (P=0.001). Additionally, there was a notable improvement in the NYHA function (P<0.001) and an enhancement in the quality of life (P=0.001). Five characteristics correlated with the lack of response to CRT were history of dobutamine usage, QRS interval (QRS) length before implantation, severe ventricular arrhythmias before implantation, atrial fibrillation after implantation, and severe ventricular arrhythmias after implantation.

Conclusions: Properly used CRT device improves heart failure symptoms, mortality, and readmissions. There are several predictors of cardiac resynchronization treatment failure. This information helps us comprehend the restricted patient group and develop better treatments, especially in low-income countries.

Keywords: Heart failure; mortality; rehospitalization; cardiac resynchronization therapy (CRT); predictors of failure

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Introduction

Background

Heart failure arises from structural abnormalities that exhibit a significant morbidity and mortality rate. Over the years, there have been novel approaches for managing heart failure that effectively decrease mortality rates (1). Nevertheless, heart failure patients who have experienced substantial loss of synergy may exhibit a poor response to appropriate pharmacological intervention (2). Cardiac resynchronization therapies (CRT) have demonstrated outstanding efficacy in the treatment of heart failure, as evidenced by numerous studies (3-5). CRT effectively lowers rates of re-hospitalization and mortality while also enhancing the overall quality of life for patients. The implantation of CRT is recommended in appropriate patients, as stated by the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/ Heart Failure Society of America (HFSA) (6) and European Society of Cardiology (ESC) (7) heart failure guidelines. The treatment objectives for this patient cohort center on reducing overall mortality, reducing readmission rates, improving clinical symptoms, and enhancing the quality of life (8).

Highlight box

Key findings

- Factors correlated with the lack of response to cardiac resynchronization therapy were history of dobutamine usage, QRS interval length before implantation, severe ventricular arrhythmias before implantation, atrial fibrillation after implantation and severe ventricular arrhythmias after implantation.

What is known and what is new?

- Cardiac resynchronization therapy (CRT) has shown effectiveness in treating heart failure. However, a report indicated that up to 30% of individuals undergoing CRT did not exhibit a response to the treatment. In Vietnam, there was a dearth of comprehensive data on the safety and efficacy profiles of CRT.
- Using a CRT device correctly can enhance heart failure symptoms, decrease mortality rates, and reduce readmissions. Multiple factors can be used to predict the failure of cardiac resynchronization treatment.

What is the implication, and what should change now?

- In low-income countries, optimizing CRT based on established predictors can lead to better resource allocation and patients care.

Rationale and knowledge gap

CRT has demonstrated efficacy in the treatment of heart failure, as evidenced by various research studies such as COMPANION, CARE-HF, and MADIT-CRT (9-11). Nevertheless, there was a report that stated 30–50% of CRT patients did not respond to the treatment (12). Numerous studies have shown factors that are linked to a lack of response to CRT (13-15): baseline factors, including the patient's age, sex, presence of underlying heart failure; any other medical conditions; New York Heart Association (NYHA) classification; prior use of inotropic therapy (dobutamine); and the use of nitrates. Laboratory results, such as hemoglobin levels and estimated glomerular filtration rate, also hold effects on outcomes. Recently, studies also show other characteristics that predict worse outcomes, including right bundle branch block morphology (16), or ischemic etiology (5), and the presence of a cardiac scar (17). On the other hand, atrial fibrillation on electrocardiogram (ECG) may potentially indicate atrioventricular (AV) node dissection and provide information on the duration of the QRS interval (QRS) complex. In developing countries, the implementation of CRT still faces several challenges, including limited financial and healthcare sources. To guarantee the successful implementation of CRT in these countries, strategic programs should prioritize the patient selection process, the awareness enhancement of its efficacy, and the availability of essential instruments. Furthermore, the performance of CRT can be supported through international partnerships and the utilization of local healthcare systems. In Vietnam, only two studies have been conducted on CRT populations with limited size, and no conclusions have been made on predictors of failure (18,19).

Objective

In Vietnam, our study is the third investigation to acquire and examine clinical outcomes in heart failure patients

who undergo CRT monitoring and is the pioneering study in Vietnam with the objective to evaluate factors that can predict failure following CRT implantation. We present this article in accordance with the STROCSS reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-408/rc).

Methods

Study setting & eligibility criteria

This is a multicenter, ambispective study that enrolled all CRT implantation patients at five hospitals in Ho Chi Minh City from April 2016 to April 2020: University Medical Center Ho Chi Minh City, Heart Institute of Ho Chi Minh City, Tam Duc Heart Hospital, Thong Nhat Hospital, and Vinmec Central Park Hospital. The retrospective process was only conducted in the Heart Institute of Ho Chi Minh City. The rest of the study was prospectively performed in all five hospitals. The decision to recruit patients in both ways was made due to concerns of slow recruitment. Patients eligible for CRT implantation were those with symptomatic heart failure (NYHA class II–IV), left ventricular ejection fraction (LVEF) ≤35%, and QRS duration ≥130 ms, as per ESC guidelines (20). Exclusion criteria included patients under 18 years of age, those unwilling to participate, and individuals with a life expectancy less than 1 year due to non-cardiac conditions. This designation was completely independent of the researcher. Firstly, cardiologists specializing in cardiovascular diseases (CVDs) would determine if the patient met the criteria for CRT implantation and then consult with arrhythmia specialists to reach a consensus. Afterwards, the highest-ranking medical authority at the hospital would make the final decision on whether or not to perform CRT implantation, once there was consensus from the patient and their family. After the implantation, the patient would continue to be monitored and treated with internal medicine, following the recommended treatment for heart failure with either the maximum or optimal dosage that the patient can tolerate. The non-pharmacological treatment regimens remained unchanged prior to device implantation.

All prospective participants would be monitored up to 1 year after discharge. This evaluation included the assessment of early (defined as complications arose within the first month after implantation) and late complications, all-cause mortality, readmission due to heart failure or other causes, as well as the evaluation of clinical and subclinical parameters such as NYHA functional class, improvement in quality of life (based on changes in the EQ-5D-5L scoring system), changes in ejection fraction, changes in left ventricular size, degree of valve regurgitation, and changes in cardiac rhythm disturbances. Patients were considered to be CRT responsive when there were improvements in clinical examination, less re-hospitalization due to cardiac causes, and no death due to cardiac reasons. There was not a consensus definition of CRT responsive. Therefore, our criteria were meant to align with other studies' definitions (9-11). Primary outcomes included rehospitalization and mortality rate 1 year after discharge. Secondary outcomes included early and late complications related to the procedure. Non-responsive post implantation was defined as follows: CRT patients who have undergone multiple follow-ups and device adjustments without any improvement in heart failure clinical presentation, resulting in re-hospitalization and mortality due to exacerbated heart failure. Major complications related to CRT implantations included access site bleeding and hematoma, lead dislodgement, infection, pneumothorax, coronary sinus perforation/dissection, cardiac tamponade, or myocardial injury among others (21). A patient was considered "stable" if all the following criteria were met: symptom improvements; follow-up ECG, echocardiography, and device check showed specific improvements (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research was approved by the Ethics Review Board of the University of Medicine and Pharmacy at Ho Chi Minh City (No. 507/ĐHYD-HĐĐĐ). All participating hospitals/institutions were informed and agreed with this study. Every patient involved in the study signed a consent form to participate.

Statistical analysis

Sample size was calculated according to event rate determined on a single population formula:

$$n = \frac{p(1-p)}{d^2} \times 1.96^2 \quad [1]$$

With (p=0.06; d=0.05), we calculated the size would be: n=87.

p: mortality rate within 1 year of CRT implantation; the value of p was obtained from the COMPANION study. Mortality rate within 1 year of cardiac resynchronization therapy defibrillator (CRT-D) and cardiac resynchronization

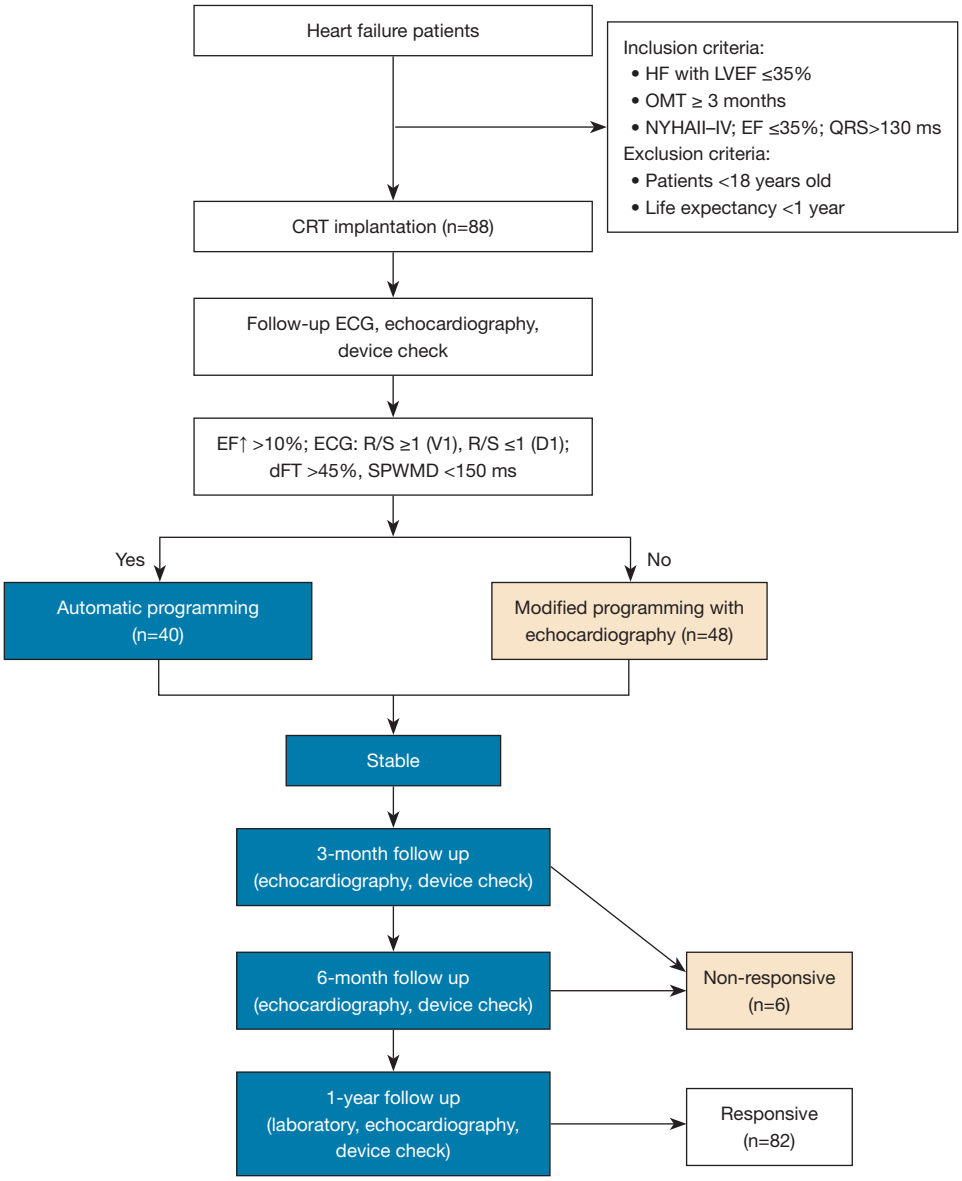

Figure 1 Study flow. CRT, cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction; OMT, optimal medical treatment; NYHA, New York Heart Association; EF, ejection fraction; QRS, QRS interval; ECG, electrocardiogram; dFT, defibrillation threshold; SPWMD, septal posterior wall motion delay.

therapy pacemaker (CRT-P) implantation was 5% and 8%, respectively (9).

d=0.05 means accepted relative error was 5% with 95% confidence interval.

The standard distribution is expressed as an average ± the standard deviation and is compared using a Student's *t*-test to evaluate the difference of two variables or an analysis of variance (ANOVA) test when the difference of many variables is needed. If the non-standard distribution is expressed as median, or put aside special circumstances, then retest by means of Skewness and Kurtosis before using Student's *t*-test. We also used McNemar's paired sample *T*-test to find the differences between the results before and after the treatment. For the purpose of this study, since we needed to do assessment forms at various times (after the procedure, after 1 month, after 3 months, after 6 months, and after 12 months), the regression method used was linear regression with multiple measurements (general linear

Table 1 Characteristics of the study population (N=88)

Characteristics	Value
Male	60 (68.2)
Age (years)	62.5±13.4
NYHA classification	
I	0
II	1 (1.1)
III	69 (78.4)
IV	18 (20.5)
BMI (kg/m^2)	22.6±2.9
Heart rate (bpm)	90.7±17
Systolic pressure (mmHg)	104.4±14
Diastolic pressure (mmHg)	65.5±7.4
HGB (g/L)	128±18
NT-proBNP (pg/dL)	3,569.9±404.9
Plasma sodium (mmol/L)	135±11.8
Plasma creatinine (mmol/L)	99.6±25
eGFR (mL/min/1.73m^2)	67.8±18.5
Left bundle branch block	87 (98.9)
Right bundle branch block	1 (1.1)
Sinus rhythm	86 (97.7)
Arrhythmias type before CRT implanting (Holter ECG)	
Atrial fibrillation episode	13 (14.8)
Non-sustained ventricular tachycardia	60 (68.2)
Sustained ventricular tachycardia	11 (12.5)
No arrhythmias	4 (4.5)
Mean QRS complex duration (ms)	155 (147.6–162.4)
Ejection fraction before implantation (%)	24±5.9
Left ventricular end-diastolic diameter (mm)	69.5±7.9
Left ventricular end-systolic diameter (mm)	58.9±7.9
Pulmonary artery pressure (mmHg)	37.8±11.4
Aortic valve maximal velocity (m/s)	1.07±0.34
Mitral regurgitation degree	
Mild	9 (10.2)
Moderate	24 (27.3)
Severe	51 (58.0)
None	4 (4.5)

Categorical variables are presented as n (%), continuous variables with normal distribution are presented as mean ± SD, and those not normally distributed are presented as median (Q1–Q3). NYHA, New York Heart Association; BMI, body mass index; HGB, hemoglobin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; QRS, QRS interval.

regression with repeated measures). This method allows the integration of different measurements into one analysis. The other characteristic was that the equation participation variables were implemented as random variables, allowing for unlimited results by the analysis sample. Analyzes were performed one by one for each resulting variable. There were two groups of resulting variables: for the binary (yes/no) group of variables, we use the logistic regression equation; for the quantitative variable, we used the regular linear regression equation to rule out confounding factors.

Data management

Due to the relatively small number of patients assigned to CRT implants, traditional linear regression using frequentist methods may not be appropriate, as some variables could fail to meet the necessary assumptions. To address this, we employed a more robust regression analysis using a Bayesian approach with the Markov chain Monte Carlo (MCMC) technique. This method allows for the incorporation of prior information and accounts for parameter uncertainty, making it well-suited for smaller sample sizes. By leveraging Bayesian regression, we can generate more reliable estimates and credible intervals, ensuring a more accurate understanding of the relationships between the variables in this context. The MCMC regression and engineering equations were programmed in the WinBUGS program, with the first 5,000 loops to set the first parameter (burn-out phase). The calculation result of 20,000 next loop was used to estimate the value of the equation parameters. To ensure the independence of calculated values, we only store the results after each of the ten calculation loops. Statistically significant threshold α=0.05. The statistical test used was test Z of the normal distribution. Within 4 years, we enrolled total of 88 CRT implantation participants, 11 of them were non-responsive.

Results

Patients characteristics and laboratory results

Over the course of a four-year study, spanning from April 2016 to April 2020, we collected data from five hospitals and documented 88 cases of successful CRT implantation. Characteristics of the study population is shown in *Table 1*.

The study included individuals ranging in age from 21 to 91 years. The age group with the highest rate of CRT implantation was 60 to 69 years, with a rate of 37.5%. The

Table 2 CRT types and implantation parameters

CRT implantation methods	Value (N=88)
CRT device	
CRT-P	26 (29.5)
CRT-D	62 (70.5)
Venous access	
Venous puncture	87 (98.9)
Thoracic surgery	1 (1.1)
Pocket location	
Subcutaneous	87 (98.9)
Submuscular	1 (1.1)
Anesthesia method	
Local anesthesia	87 (98.9)
General anesthesia	1 (1.1)
Right ventricular lead	
Apical	30 (34.1)
Septal	58 (65.9)
Right atrial lead	
Auricle	53 (60.2)
Atrial septal wall	35 (39.8)
Left ventricular lead	
Posterolateral	23 (26.1)
Posterior	30 (34.1)
Lateral	34 (38.6)
Epicardial	1 (1.1)
Implantation duration (minutes)	144.8±28.8 [60–210]

Data are presented as mean ± SD [Q1–Q3]. CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker.

male-to-female ratio of patients receiving a CRT implant was 2:1. There was no statistically significant difference in the mean age at which CRT implantation occurs between males and females (P=0.4). The majority of patients were NYHA III or IV at admission. There was only one patient with NYHA II heart failure to get CRT implantation due to severe left ventricular end-diastolic dilatation (100 mm), LVEF of 10% and ventricular arrhythmias.

There were 83 patients (94.3%) who had undergone coronary angiography. We noted that 50% of CRT patients had secondary dilated cardiomyopathy heart failure, which was caused by hypertension, diabetes, alcohol abuse, arrhythmias, and after valvular surgery. There were 42% of CRT patients with primary dilated myocardiopathy heart failure. Only 8% had heart failure due to ischemic heart disease. Three patients were performed percutaneous coronary intervention, while the other two had coronary artery bypass grafting (CABG) and the rest were medically treated due to small coronary artery size and extensive lesions. These seven patients were closely monitored after discharge with titrated medications when suitable. After 6 months, they did not improve clinically. Therefore, we decided to perform CRT on them.

The heart failure medications were used during inhospital phase included beta blockers (77.3%), angiotensin-converting enzyme inhibitor (ACEI) (59.1%), angiotensin receptor neprilysin inhibitor (ARNI) (2.3%), angiotensin ii receptor blockers (ARB) (38.6%), magnetic resonance angiography (MRA) (72.7%), sodium-glucose cotransporter 2 inhibitor (SGLT2i) (13.4%), digoxin (76.1%) and furosemide (96.6%). Digoxin usage rate was high, basically due to the traditional way of heart failure description in the country.

CRT technical parameters

Among 88 participants, there was one case we were unable to implant the left ventricular electrical wire into the coronary sinus. Therefore, we had to perform thoracic surgery to get to the left ventricle and implant the wire into the epicardial layer. Specific parameters of all the CRT procedures are shown in *Table 2*. *Figure 2* also displays a representative case of CRT implantation in the study.

Effective profile of CRT implantation

NYHA classification, heart rate and LVEF changes after CRT implantation

We obtained NYHA classification information in 82/88 patients (93.2%) at 1-year follow up (6 patients died during the first year). NYHA classification improved significantly (one NYHA II, one NYHA III and two NYHA IV cases stayed the same. One NYHA III case progressed to NYHA IV; 64 cases shifted from NYHA III to NYHA II/I; 13 cases migrated from NYHA IV to NYHA III/II; by conducting a McNemar test P<0.001) (*Table 3*).

Heart rate and LVEF improved significantly beginning

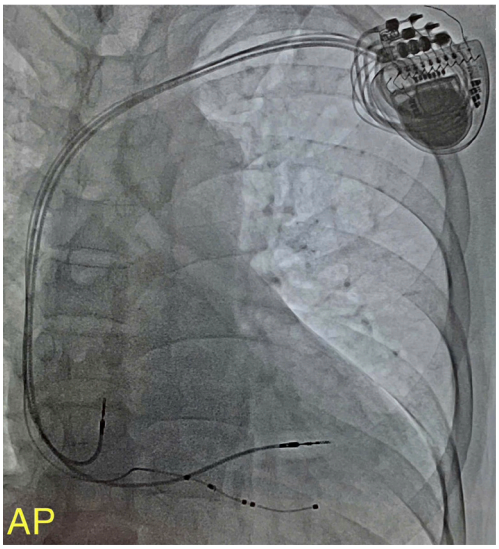

Figure 2 Final fluoroscopy image of one CRT implantation case in the study. CRT, cardiac resynchronization therapy; AP, anterior-to-posterior.

Table 3 The NYHA classification after 1-year CRT implantation (n=82)

Before implantation	1 year after implantation			
	I	II	III	IV
II	0	1	0	0
III	5	59	1	1
IV	0	10	3	2

NYHA, New York Heart Association; CRT, cardiac resynchronization therapy.

3 months after implantation and continuing thereafter (*Table 4*).

Quality-of-life score changes after CRT implantation

Quality of life (*Table 5*) increased significantly after CRT implantation according to EQ-5D-5L score changes (P=0.001).

All-cause mortality and rehospitalization rate

We were able to follow up with all 88 of the enrolled participants. We noted 11 deaths (12.5%), six of them happened within 1 year (6.8%) after implantation, five others happened after 1 year (5.7%).

As shown in *Figure 3*, 100% patients were hospitalized at least one time due to heart failure before CRT implantation. There was significant decreasing in rehospitalization rate 1 year after implantation compared to their own rehospitalization rate before implantation (P=0.001).

Safe profile and predictors of non-response to CRT

Safe profile of CRT implantation

In terms of early complications, there was no report of

Table 5 Quality-of-life score based on EQ-5D-5L score before and after implantation

	Before implantation	1 year after implantation	P
EQ-5D-5L score	0.451±0.045	0.734±0.038	0.001

Data are presented as mean ± standard deviation.

Table 4 Heart rate and LVEF changes before and after CRT implantation (N=82)

Assessment time	Mean	Standard deviation	Median	Minimum	Maximum	P
Heart rate (beats per minute)						
Before implantation	90.7	17.7	92	84	132	
1 week after implantation	88.7	12.2	90	74	126	0.16
3 months after implantation	86.8	10.7	87	70	118	0.02
6 months after implantation	83.5	9	84	60	102	<0.001
1 year after implantation	80.8	8.4	81	60	106	<0.001
LVEF (%)						
Before implantation	24	5.9	25	10.0	35	
1 week after implantation	27.7	6.8	28	7.0	41	<0.001
3 months after implantation	32.1	6.6	34	15	52	<0.001
6 months after implantation	36.6	7.9	37	19	58	<0.001

LVEF, left ventricular ejection fraction; CRT, cardiac resynchronization therapy.

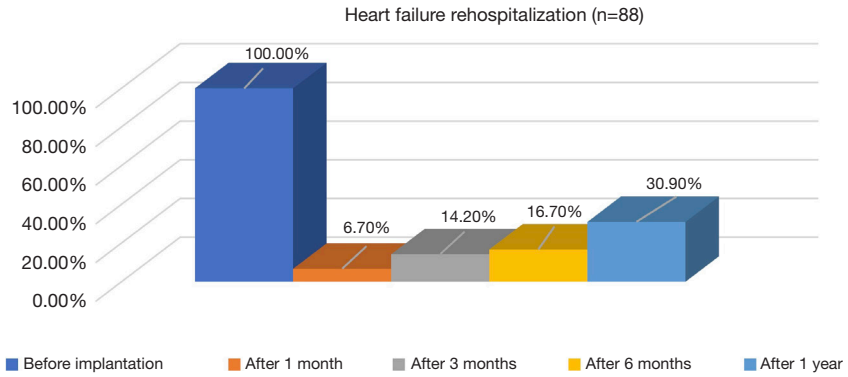

Figure 3 Heart failure rehospitalization rate before and after CRT implantation. CRT, cardiac resynchronization therapy.

Table 6 Early and late complication after CRT implantation

Complications	Number of patients	Rate (%)
Early complication (N=88)		
Cardiac arrest	0	0
Cardiac perforation requiring emergent surgery	0	0
Pericardial effusion	0	0
Pleural effusion	1	1.1
Infection	2	2.3
Device pocket hematoma	2	2.3
Dislocated electrode	2	2.3
Ventricular arrhythmias	1	1.1
No complications	80	90.9
Late complication (N=88)		
Inappropriate shock	14	15.9
Atrial fibrillation	11	12.5
Sinus tachycardia	3	3.4
Electrical storm	3	3.4
No complications	57	64.8

CRT, cardiac resynchronization therapy.

cardiac arrest, heart perforation, or pericardial effusion. There were eight early complication instances (9.1%) following CRT implantation, including one pleural effusion, two infections, two hematomas, two lead dislodgement, and one ventricular arrythmia occurrence. All early problem cases were successfully handled and discharged. Late complications after CRT implantations were mostly due to inappropriate shocks (*Table 6*). In addition, there were 3/88 cases (3.4%) with electrical storms due to worsening heart failure. No electrical storm appeared due to CRT-D device.

Mortality-related factors (non-responsive factors)

We performed multivariate analysis using a linear regression model using the frequency or regression method with the Bayesian approach (*Table 7*).

Five factors were associated with CRT non-responsiveness that led to fatalities: history of dobutamine usage, QRS length before implantation, severe ventricular arrhythmias before implantation, atrial fibrillation after implantation, and severe ventricular arrhythmias after implantation. Pre-implantation arrhythmias burden was recorded based on routine ECG and 24-hour Holter ECG, which consisted of non-sustained ventricular tachycardia (68.2%), sustained ventricular tachycardia (12.5%), torsade de pointes (1.1%) and ventricular fibrillation (2.3%).

Discussion

During the research period from April 2016 to April 2020, at five hospitals (University Medical Center Ho Chi Minh City, Heart Institute of Ho Chi Minh City, Tam Duc Heart Hospital, Thong Nhat Hospital, and Vinmec Central Park Hospital), we recruited 88 successful cases of implanting the device that met the study conditions. After the implantation, patients continued to be monitored and treated as standard regimens for heart failure treatment as recommended.

Our study revealed that 87.5% of patients exhibited a positive response to a CRT. A 2022 study by experts from the Republic of Moldova showed that CRT yields excellent outcomes in heart failure patients, particularly noting a

Table 7 Mortality outcome and related factors

Factor	P	OR	Confidence interval
Age	0.78	0.9	0.8–11.0
Sex	0.78	3.2	0.3–16.8
NYHA classification	0.06	3.4	0.22–14.4
Dilated cardiomyopathy or ischemic heart failure	0.07	0.4	0.2–9.6
Creatinine clearance before implantation	0.19	1.1	0.9–11.0
Ejection fraction before implantation	0.64	5.8	0.3–12.4
Type: CRT-D or CRT-P	0.6	3.36	0.25–9.4
Left ventricular wire location	0.65	3.2	0.35–11.4
History of dobutamine usage	0.0001	14.7	10.8–42.1
Ventricular arrhythmias burden before implantation	0.0001	10	2.9–39.8
QRS length before implantation	0.006	4.8	2.1–19.6
Atrial fibrillation after implantation	0.001	10.5	6.7–28.9
Severe ventricular arrhythmias after implantation	0.0001	5	1.7–19.5

OR, odds ratio; NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; QRS, QRS interval.

decreased death rate in individuals with left bundle branch block and reduced ejection fraction (4). In the same year, the authors of the LOT-ICD trial revealed cost-effective outcomes concerning CRT in patients indicated for CRT-D. They also reported less fluoroscopy duration and radiation exposure (22). Currently, there is no universal definition for responsive CRT implantation (23). The most common used definition for non-responsive is adapted for CRT patients who have undergone multiple follow-ups and device adjustments without any improvement in heart failure clinical presentation, resulting in re-hospitalization and mortality due to exacerbated heart failure. In our study, a total of 6 patients died within the first year, while five patients died within the second year after discharge. To compare with similar studies, Higgin's study involving 245 patients reported a response rate of 74% (24). Similarly, Young *et al.*'s study (25) with 187 patients reported a machine response rate of 70%. Other studies conducted by Molhoek *et al.* and Yeim *et al.* also yielded comparable results (26,27). The meta-analysis conducted by Varma *et al.* included a total of 1,327 patients, with a response rate of 83% to CRT (28). Our study observed greater response rates, potentially due to a variation in patient selection. This could be attributed to the fact that the cost of equipment is exorbitant, leading clinicians to prioritize transplant patients, particularly those with type IA designations. Besides, our study found that the percentage of individuals suffering from heart failure due to ischemic heart disease was quite small, approximately 8%. Studies proved that, although ischemic cardiomyopathy resolved its cause, the prognosis of improved treatment of heart failure, particularly the response to CRT, was also generally poorer for patients with dilated cardiomyopathy (11,13). Varma *et al.* found that the presence or absence of a CRT response in a group of patients with heart failure due to dilated cardiomyopathy was better than that of patients with heart failure due to ischemic heart disease (P=0.003) (28). This is primarily due to the presence of old scar tissue in the affected region of the heart, which renders it unresponsive even if the electrode is placed in an area previously affected by a heart attack. Consequently, achieving resynchronization through the use of the machine is highly unlikely in such cases (29,30). The co-morbidity of heart failure also played a significant role in CRT patients' outcomes. Specifically, diabetes could affect clinical outcomes (31,32), via negative effects exerted at level of device functionality (33), and at epigenetic level (34). Even the hyperglycemic condition alone can affect CRT response at 1 year after adjusting for other confounders such as age, diabetes, and hypertension (35).

Among the total of 88 patients enrolled in our study, there were 86 patients (97.7%) who implanted a CRT

with a sinus rhythm. There were two patients who had paroxysmal atrial fibrillation, which accounted for 2.3%. According to the current heart failure guidelines (6,7), class IIa is recommended for CRT implantation in patients with paroxysmal or refractory atrial fibrillation. In a study by Gasparini *et al.*, after a 4-year follow-up, patients with CRT-implanted atrial fibrillation showed minimal improvement in their ejection fraction, left ventricular diameter, or functional symptoms (36). However, there was something really interesting about this study: if they had an AV nodal conduction cut, then this group of patients would still have a good response to the CRT in nearly a group of patients with a sinus rhythm (36). Additionally, if we programmed the CRT such that the left ventricular tachycardia was greater than 98%, patients with atrial fibrillation still responded well to the CRT (37). Thus, for patients with atrial fibrillation, we consider selecting a programmable left ventricular response when atrial fibrillation is present. This new programming method has been around for 3 years, thanks to the adaptive CRT feature, which has increased the CRT response rate by 46% (38).

The response to a CRT implantation is contingent upon several variables, including the patient's pre-implanted medical condition, the type of CRT chosen, the position of the left ventricular electrode, and the occurrence of arrhythmias after implantation. Recently, Sardu *et al.* (39) reported the role of endothelial dysfunction in the response of heart failure patients with CRT implantation. They investigated a new biomarker, serum miR-130a-5p, in predicting CRT response, and the result was promising. However, the most critical determinant in enhancing the CRT's response rate is the proficiency of the machine programming team in delivering optimal results. In the event that the CRT was programmed autonomously and the patient exhibited signs of non-compliance, a reevaluation would be necessary to determine the cause of the failure. The proportion of patients who initially do not respond to CRT is approximately one-third, according to a study (40). Forty-eight patients (54.5%) in our study did not respond initially; therefore, the CRT had to be reprogrammed. This implies that one patient had to be reprogrammed for every two patients. The reason that the CRT does not respond is a challenging one to explain. However, the response of the CRT may be limited by the following: individuals diagnosed with coronary artery disease exhibit a reduced level of responsiveness in comparison to those without the condition (41). A positive correlation exists between the width of the QRS and response quality. Additionally, the absence of left bundle branch block or atrial fibrillation prior to or following machine implantation can impact response rates. Three significant causes of inadequate response to initial CRT were identified in our study: patients who had received a dobutamine dose prior to this one (P=0.002), high levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (P=0.004), and low LVEF (P=0.007). When the patient exhibits no clinical improvement, no change in NYHA ratings, and no improvement in left ventricular function, it is advisable to modify the CRT (42). In order to improve response rate or achieve a better result than the initial one, the following adjustments should be made to the ECG or echocardiography equipment: QRS width should not decrease, ECG should not exhibit R/S $\geq$1 in V1 or R/S $\leq$1 in D1, echocardiography should reveal an ejection fraction (EF) improvement of less than 20% over the initial EF, defibrillation threshold (dFT) should shorten to 45% of the EA wave, and septal-to-posterior wall motion delay should exceed 150 Ms. Another aspect that could affect CRT response and lead to better clinical outcomes is angiotensin receptor/neprilysin inhibitor (ARNI) usage (43). Main effects are due to anti-remodeling effects via the modulation of epigenetic pathways (43) and the reduction of inflammatory burden, which is tightly linked to CVD and worse clinical outcomes (44). Two patients received ARNI in our study. The limited quantity is attributable to the lack of popularity of ARNI in Vietnam during this investigation.

In our study, the mean ejection fraction was 24%, with a maximum of 35% and a minimum of 10%. This outcome aligns with global studies, which report an average EF within the range of 23–29%, including the PROSPECT study (13) and the research conducted by Varma *et al.* (28). Post-CRT implantation, the mean ejection fraction improved, with an average EF of 27.7% at 3 months, 32.1% at 6 months, and 36.6% at 1 year, demonstrating statistical significance (P<0.001). This indicated that the ejection fraction significantly altered following CRT implantation and progressively improved over time, contingent upon the patient's favorable response to the device. The ejection fraction results in our study seem to exceed those reported in some of the aforementioned studies. This may be attributed to the fact that, in our investigation, patients assigned to implanted CRT exhibited a decreased incidence of ischemic cardiomyopathy compared to the other studies. Sherazi *et al.*'s research indicates that CRT enhances left ventricular function (45). The mean end-diastolic left ventricular diameter in our study was 69.5 mm, while the mean end-systolic left ventricular diameter was 58.9 mm.

After 1 year, the mean end-diastolic left ventricular diameter is 67.81 mm, with a statistically significant difference (P=0.009). The mean end-systolic left ventricular diameter is 51.48 mm, also demonstrating a statistically significant difference (P<0.001). The CRT has demonstrated the ability to reverse left ventricular anatomy, enhancing the size of the left heart chamber. Structural alterations in the left ventricle become apparent by the third month and progressively intensify from the sixth month, with further prolongation observed subsequently, as demonstrated by the CARE-HF study.

Our research indicates a significant correlation between the lack of response to CRT and various factors that contribute to the persistence of heart failure. These factors include the extent of the QRS complex before implantation of the device, the use of dobutamine as a precursor, the presence of a severe ventricular rhythm disturbance prior to implantation, the occurrence of paroxysmal atrial fibrillation after implantation, and the presence of severe ventricular arrhythmias after implantation. It is well understood that a patient who succumbs to heart failure is influenced by numerous factors. The utilization of dobutamine is associated with adverse outcomes following CRT installation. This outcome parallels the study conducted by Varma *et al.* (28). The study had 1,327 patients, of whom 107 received dobutamine (8.1%), and 30 did not react to cardiac resynchronization therapy (CRT) (38.9%, P=0.029). Hansky *et al.* (46) have proposed that CRT implantation in unstable heart failure patients may result in poorer outcomes. The QRS length prior to implantation is globally recognized as an independent predictor of mortality in individuals with significantly reduced ejection fraction. QRS duration exceeding 150 ms typically shows a favorable response to CRT compared to the cohort with QRS duration less than 150 ms in the COMPANION, CARE-HF, and MADIT-CRT investigations (9-11). Consequently, an enhancement in QRS duration serves as a reliable predictor and correlates with increased survival rates in heart failure patients exhibiting lower ejection fraction and prolonged QRS duration. Conversely, ventricular arrhythmia has been demonstrated to correspond with poorer outcomes in heart failure (47-49). A significant incidence of ventricular arrhythmia exists in heart failure patients with decreased ejection fraction. In most instances, ventricular arrhythmia is a consequence of heart failure resulting from myocardial damage, however it can potentially precipitate heart failure. Patients with advanced heart failure commonly utilize certain drugs that may increase the risk of arrhythmias: digoxin and dobutamine (50). This ventricular arrhythmia can result in abrupt cardiac death in heart failure and also exacerbates adverse outcomes. In the meta-analysis conducted by Varma *et al.* involving 1,327 patients, the prevalence of atrial fibrillation prior to and following CRT implantation was 38.4%. A statistically significant difference in response to CRT was observed between the two groups, with P=0.002 (28). Heart failure is a distinct risk factor for atrial fibrillation, exhibiting an odds ratio of 3.2. New-onset atrial fibrillation exacerbates heart failure, as evidenced by peak oxygen consumption exceeding that of anaerobic metabolism (51). Atrial fibrillation elevates mortality in heart failure patients by 2.7 in males and 3.1 in females. Atrial fibrillation in CRT patients impedes left ventricular function, resulting in a lack of response to CRT. These data lead to the conclusion that atrial fibrillation is a risk factor for increased mortality in patients undergoing CRT implantation. Should we be able to anticipate atrial fibrillation post-implantation, it is advisable to contemplate AV nodal ablation prior to CRT implantation. In the presence of atrial fibrillation following CRT installation, prompt consideration of AV nodal ablation is advised. We should select newer generation CRT devices that incorporate atrial fibrillation reduction programming to identify patients at a higher risk of developing atrial fibrillation following CRT implantation.

Furthermore, the patient's reaction to CRT is influenced by various parameters, including the specific type of CRT machine and the features of the left ventricular electrodes. These factors contribute to the improvement of the patient's readmission and mortality rates (28). The favorable outcome of this study advocates for the integration of CRT into clinical practice in Vietnam. The scarcity of accessible data on CRT in a developing nation has impeded clinicians from translating knowledge into practice. The increased cost was also a factor in the feasibility of changing clinical guidelines for CRT in heart failure patients. We believe that the favorable results and precise linkages between particular population features and outcomes will significantly influence clinical guidance. Consequently, we would witness enhancements in CRT accessibility and routine practice.

The study was subject to several limitations. To begin with, the study's ambispective nature, not having a control group, and the limited sample size restricted its ability to make significant recommendations. The limited sample size also did not reflect the underused CRT situation in female patients, despite the well-established benefit in this subgroup (52). While the method remains accurate in terms of

study approaches, we believe it is appropriate to undertake this study to highlight which patient groups should be given even more cautions, as CRT have been given clear indication in heart failure recommendations. Additionally, there is a possibility that some of the collected information may be not sufficiently accurate and may be with missing information, particularly with the medication dosage. The timing of patient follow-up is inconsistent, with some patients having received CRT for several years. Besides, while some patients had just undergone CRT implantation, others exhibited significant variability in their data collection. Finally, due to missing data, we could not obtain the medical treatment post-implantation. Future research is needed, especially in an older population and for a longer follow-up period.

Conclusions

This study retained its status as the most extensively conducted study in Vietnam, a country with a low-income level. When utilized correctly, the insertion of a CRT device holds the capacity to substantially reduce symptoms, mortality rates, and the probability of readmission in patients afflicted with heart failure. Several indicators can be indicative of a lack of response to cardiac resynchronization therapies: previous administration of dobutamine, increased QRS complex width, occurrence of ventricular arrhythmias before or after CRT placement, and the development of atrial fibrillation following CRT placement. This information enables us to gain a deeper comprehension of the distinctive attributes of the restricted patient cohort, facilitating the implementation of more pertinent interventions in subsequent instances.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research was approved by the Ethics Review Board of University of Medicine and Pharmacy at Ho Chi Minh City (No. 507/ĐHYD-HĐĐĐ). All participating hospitals/institutions were informed and agreed with this study. Every patient involved in the study signed a consent form to participate.

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