



The Interaction Between Tricuspid Regurgitation and Cardiac Resynchronization Therapy Response in Patients with Congestive Heart Failure

Babak Payami ^{1,*}, Elham Mohammadyari¹, Shahla Madjidi¹ and Arezou Zoroufian ²

¹Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Email: babakpayami@yahoo.com

Received 2023 June 11; Revised 2023 September 03; Accepted 2023 September 18.

Abstract

Background: Aggravation of tricuspid regurgitation (TR) is a predictable issue following cardiac device implantation, while its clinical importance is subject to debate.

Objectives: We aimed to recognize the alteration of TR following cardiac resynchronization therapy (CRT) and its effect on the response to CRT.

Methods: In this prospective study, 70 candidates were recruited for CRT from those who visited two university hospitals in Tehran and Ahvaz (Iran) from January 2012 to March 2013. Baseline specifications were recorded for all the participants. All the patients underwent echocardiography before and 6 months after CRT administration. They were then divided into two categories for further comparison: (1) Patients with no or mild TR and (2) patients with moderate-to-severe TR. The echocardiographic response to CRT was defined as a left ventricular end-systolic volume (LVESV) decrease of >15% or left ventricular ejection fraction (LVEF) advancement of >5%. The clinical response to CRT was one class improvement based on the New York Heart Association (NYHA) class.

Results: Of the patients, 24 had moderate-to-severe TR. Although the increase in cases with moderate-to-severe TR after CRT was not significant, the aggravation of TR degree after the procedure was significant ($P = 0.002$). Moreover, the NYHA class significantly improved after the CRT ($P = 0.02$). The number of cases with a clinical response to CRT based on improvement of the NYHA class was significantly greater in patients with no TR or mild TR at baseline ($P = 0.003$). There was no significant variation in response to CRT among patients who experienced TR exacerbation after CRT compared with those who had no change or a reduction in TR.

Conclusions: This study demonstrated that TR severity was exacerbated following CRT, but this alternation in TR severity had no significant effect on the response to CRT. Therefore, the presence and development of TR before and after CRT must not affect the criteria for choosing cardiac resynchronization therapy for appropriate patients.

Keywords: Cardiac Resynchronization Therapy, Tricuspid Regurgitation, Heart Failure

1. Background

Cardiac resynchronization therapy (CRT) has become a standard option for treating patients with reduced left ventricular systolic function and prolonged QRS complexes (1, 2). Based on the presence or absence of defibrillation capacity, this therapy can be classified into CRT-D (with a defibrillator) and CRT-P (without a defibrillator). Cardiac resynchronization therapy reverses the remodeling of the left ventricle and improves clinical symptoms by enhancing left ventricular systolic function. This reduces mortality and increases the survival of

patients with chronic heart failure (3). However, only 60 - 70% of the patients respond well to CRT. Note that this therapy is both invasive and expensive; thus, it seems necessary to provide selection criteria for CRT (4, 5).

Several echocardiographic characteristics were proposed as predictive factors for the response to CRT, but none was selected as a proper indicator (6). Tricuspid valve regurgitation (TR) is a common observation in echocardiography. The prevalence of TR in the general population varies from 15 to 100% due to different definitions of TR and the studied populations

(7). In patients with congestive heart failure (CHF), moderate-to-severe TR is observed in up to 60% of the patients (8). Severe TR can independently predict survival in patients with a low left ventricle ejection fraction (LVEF) (9). Aggravation of TR is a comprehensible complication after cardiac device implantation; however, its clinical importance is subject to debate (10).

In some studies, the progression of mild TR to severe TR following CRT and the presence of significant TR before implantation without improvement after CRT was associated with all-cause mortality (11). A study concluded that exacerbation of TR after CRT is a predictor of worse clinical and echocardiographic response but was not significantly associated with reduced survival despite better clinical and echocardiographic response after CRT (12). Therefore, it is necessary to investigate the changes in TR following CRT and its association with the response to CRT.

The NYHA (New York Heart Association) classification serves as a fundamental tool for heart failure risk stratification and determines clinical trial eligibility for drugs and devices (13). The NYHA functional class helps classify CHF patients based on their symptoms:

Class I: No symptoms of heart failure

Class II: Symptoms of heart failure with moderate exertion, such as ambulating two blocks or two flights of stairs

Class III: Symptoms of heart failure with minimal exertion, such as ambulating one block or one flight of stairs, but no symptoms at rest

Class IV: Symptoms of heart failure at rest

2. Objectives

We aimed to identify the changes in TR following CRT and its effect on response to CRT in patients who visited two university hospitals in Iran.

3. Methods

3.1. Study Population and Criteria

In this prospective study, we registered candidates for CRT who visited the Tehran Heart Center (Tehran University of Medical Sciences, Tehran, Iran) and Imam Khomeini Hospital (Jundishapur University of Medical Sciences, Ahvaz, Iran) between January 2012 and March 2013. The inclusion criteria were: (1) Symptomatic CHF, NYHA classes III and IV, with no response to pharmacological treatment; (2) ejection fraction (EF) $\leq 35\%$; (3) QRS complex > 120 msec; age > 18 years. The exclusion criteria were (1) right bundle branch block; (2) previous pacemaker

implantation; (3) survival < 1 year; (4) severe renal failure (serum creatinine > 3 mg/dL); (5) atrial fibrillation rhythm at presentation.

The participants provided written informed consent before enrolment. The study protocol was approved by the Institutional Committee of Medical Ethics and the Research Board of both universities (IR.AJUMS.REC.1392.115). This study adhered to the essentials outlined in the Declaration of Helsinki.

3.2. Demographic and Clinical Data

Baseline characteristics, including demographic data, medical history, and physiological measurements, were recorded for all the participants in face-to-face interviews during admission. Based on our institutional definitions adopted from international guidelines (14), a positive history of hypertension was established in patients who already took antihypertensive medications or had two blood pressure readings $\geq 140/90$ mmHg not less than 5 minutes apart in the sitting stance. Diabetes mellitus was positive in the patients with a definite history of diabetes and therapy with glucose-lowering agents, fasting plasma glucose ≥ 126 mg/dL, or two-hour postprandial glucose ≥ 200 mg/dL.

3.3. Echocardiography

Echocardiography was performed with a commercially available GE Vivid 3 (General Electric Healthcare, Milwaukee, WI, USA) and a 1.7–3.4 MHz probe. All the patients underwent echocardiography before and 6 months after CRT insertion. Left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured with Simpson's method. The severity of TR was assessed by regurgitation jet measurement compared to the right atrial area in apical four-chamber, parasternal short axis, and subcostal views. A TR lower than 20% was considered mild, between 20–40% was moderate, and more than 40% was severe. The anatomy of the tricuspid valve and the presence and degree of TR were also evaluated. The patients were then categorized into two groups for further comparisons: (1) Patients with no or mild TR and (2) patients with moderate-to-severe TR.

3.4. Response to CRT

The echocardiographic response to CRT was characterized as LVESV reduction $>15\%$ or LVEF elevation $>5\%$, while the clinical response to CRT was defined as one class improvement based on the NYHA class.

3.5. Statistical Analysis

The continuous variables were expressed as mean \pm standard deviation (SD) and were compared using the Student's *t*-test between the TR-positive and TR-negative groups. Analysis of variance (ANOVA) was used to compare the subgroups. Categorical variables were described using occurrence and percentage and were compared among the above-mentioned groups via the chi-square or Fisher's exact test, where applicable. P-values less than or equal to 0.05 were considered significant. PASW Statistics v. 18.0 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analyses.

4. Results

We enrolled 70 CRT candidates (mean age = 59.6 ± 10.8 ; 42 [60.0%] males) who met our criteria. Sixty-nine patients (98.6%) received CRT-D, and only one patient (1.4%) received CRT-P. Based on the baseline echocardiography, 24 cases had moderate-to-severe TR. The demographic and baseline clinical characteristics of the population are depicted in [Table 1](#).

Table 1. Baseline Characteristics of the Study Population ^a

Characteristic	Values (n = 70)
Age (y)	59.6 \pm 10.8
Male gender	42 (60.0)
CRT type	
CRT-D	69 (98.6)
CRT-P	1 (1.4)
Diabetes	21 (30.0)
Hypertension	32 (45.7)
Coronary angiography	
Normal	34 (48.6)
CAD	36 (51.4)

Abbreviations: CAD, coronary artery disease; CRT, cardiac resynchronization therapy; SD, standard deviation.

^a Values are expressed as No. (%) or mean \pm SD.

Functional echocardiographic characteristics showed significant improvements following CRT, as summarized in [Table 2](#). Although the increase in the number of patients with moderate-to-severe TR following CRT was not significant, the exacerbation of TR degree after the procedure was significant ($P = 0.002$). Moreover, the NYHA class significantly improved after the CRT ($P = 0.02$).

The number of patients who had a clinical response to CRT based on the improvement in NYHA class was significantly higher among those who had no or mild TR at

baseline ($P = 0.003$). Furthermore, the echocardiographic response to TR based on LVEF improvement was significantly lower in patients with moderate-to-severe TR ($P = 0.001$). However, the frequency of patients who had LVESV reduction following TR was not significantly different between the two groups ([Table 3](#)). Based on the TR observed in the post-CRT echocardiography, only the clinical response to CRT was significantly higher in patients who did not have TR following CRT. Tricuspid valve regurgitation was exacerbated in 23 (33%) patients following the procedure. Exacerbation of TR following CRT had no significant effect on the clinical and echocardiographic response to CRT ([Table 3](#)). The comparison of the clinical and echocardiographic response to CRT based on the degree of TR before or after CRT implantation is presented in [Table 4](#).

5. Discussion

We observed that TR is common among CHF patients who are candidates for CRT, and it is sometimes exacerbated following CRT implantation. Moreover, clinical and echocardiographic response to CRT was higher in patients who did not have TR. Tricuspid regurgitation may develop from a primary tricuspid valve deformity, raised pulmonary artery pressure, and/or right ventricular (RV) dysfunction, with dilatation of the tricuspid valve annulus (15, 16). In the present study, mild or more TR was found in 60 (85.7%) patients. This high prevalence can be attributable to advanced prolonged CHF (17). Additionally, some subjects had RV and LV dysfunction simultaneously. We detected that moderate or severe TR was an independent antecedent of echocardiographic nonresponse to CRT (10).

Patients with moderate or severe TR had higher end-systolic pulmonary artery pressure, greater RV dysfunction, and lower LVEF. These patients failed to show improvement in LV structure and function (10). Of our cases, 24 (34%) had moderate-to-severe TR, which is comparable with the study by Stassen et al. (11), in which 22% of the patients had moderate-to-severe TR. Pacing leads passing the tricuspid valve can produce or aggravate TR. New onset or exacerbated TR after lead implantation may happen due to the involvement of the tricuspid valve apparatus, leaflet perforation, or fibrosis and further cohesion of the lead to the leaflets (18, 19). Tricuspid valve regurgitation can also be a consequence of RV pacing with no direct effect of the lead on the valve structure and function (20). New onset or magnified TR after pacing or defibrillator lead implantation has been described in up to 24.2% of the patients in one study (10).

Table 2. Comparing the Echocardiographic and Clinical Variables Before and After CRT Insertion ^a

Characteristic	Pre CRT	Post CRT	P-Value
LVEF ^b	23.0 ± 6.5	27.9 ± 8.2	< 0.001
LVESV (mm) ^b	161.5 ± 69.3	140.1 ± 63.9	< 0.001
LVOT-VTI (cm) ^b	13.7 ± 3.9	15.42 ± 3.9	< 0.001
Moderate to severe TR	24 (34.2)	30 (42.8)	0.14
TR severity ^c			0.002
Normal	10 (14.3)	1 (1.4)	
Mild	36 (51.4)	39 (55.7)	
Moderate	19 (27.1)	19 (27.1)	
Severe	5 (7.1)	11 (15.7)	
NYHA class ^c			0.02
I	0 (0)	26 (37.1)	
II	0 (0)	32 (45.7)	
III	54 (77.1)	7 (10.0)	
IV	16 (22.9)	5 (7.1)	

Abbreviations: LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVOT-VTI, left ventricular outflow tract-time velocity integral; NYHA, New York heart association; TR, tricuspid regurgitation.

^a Values are presented as No. (%) or mean ± SD.

^b Paired Sample *t*-test was used.

^c Chi-square test was used.

Table 3. Clinical and Echocardiographic Response to CRT Based on the Presence of TR Before or After CRT Insertion

Characteristic	TR-	TR+	P-Value
Pre-CRT TR	(n = 46)	(n = 24)	
NYHA class improvement	43 (93.5)	16 (66.7)	0.003
LVEF improvement	32 (69.6)	7 (29.2)	0.001
LVESV reduction	22 (47.8)	8 (33.3)	0.24
Post-CRT TR	(n = 40)	(n = 30)	
NYHA class improvement	38 (95.0)	21 (70.0)	0.004
LVEF improvement	25 (62.5)	14 (46.7)	0.18
LVESV reduction	21 (52.5)	9 (30.0)	0.06

Abbreviations: CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York heart association; TR, tricuspid regurgitation.

Patients with implantable cardioverter-defibrillators (ICDs) have an excessive amount of worsened TR compared to those with pacemakers. Moreover, the position of the ventricular leads can influence the valve mechanics. It has also been shown that right ventricular outflow tract pacing is a safe site for implanting ventricular leads and could reduce the probability of valvular changes after pacing, compared with the right ventricular apex position (21). Therefore, several factors can influence the structure and function of heart valves during CRT implantation and thereby alter the response to CRT; still, as shown in our study, exacerbation of TR after device implantation does

not reduce the response to CRT. The number of moderate and severe TR cases increased in our study after CRT implantation (from 24 to 30), unlike the decrease in the number of moderate and severe TR after CRT implantation in Stassen et al.'s study (11).

The present study showed improvement in NYHA class even with TR exacerbation, while the study by Stassen et al. showed an increase in all-cause mortality with TR exacerbation (11). Raed Abu Sham'a et al. (Europace 2013 Feb) (10) also evaluated the effects of tricuspid valve regurgitation on clinical and echocardiographic outcomes in patients with cardiac

Table 4. Clinical and Echocardiographic Response to CRT Based on the Degree of TR Before or after CRT Insertion

Characteristic	Normal	Mild TR	Moderate TR	Severe TR	P-Value
Pre-CRT TR	(n = 10)	(n = 36)	(n = 19)	(n = 5)	
NYHA class improvement	9 (90.0)	34 (94.4)	14 (73.7)	2 (40.0)	0.007
LVEF improvement	6 (60.0)	26 (72.2)	6 (31.6)	1 (20.0)	0.01
LVESV reduction	5 (50.0)	17 (47.2)	7 (36.8)	1 (20.0)	0.2
Post-CRT TR	(n = 1)	(n = 39)	(n = 19)	(n = 11)	
NYHA class improvement	1 (100)	37 (94.9)	16 (84.2)	5 (45.5)	0.001
LVEF improvement	0 (0)	25 (64.1)	11 (57.9)	3 (27.3)	0.11
LVESV reduction	0 (0)	21 (53.8)	7 (36.8)	2 (18.2)	0.12

Abbreviations: CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York heart association; TR, tricuspid regurgitation.

resynchronization therapy and concluded that the presence of baseline moderate-to-severe TR was associated with increased mortality but did not predict the clinical or echocardiographic response to CRT. Patients with worsened TR following CRT are less likely to clinically respond to CRT, but as shown in our study, the exacerbation of TR after device implantation does not diminish the response to CRT.

5.1. Study limitations

This study had some limitations. First, data on the symptoms and signs of right heart failure were not methodically collected and included. We did not collect clinical data on chronic obstructive lung disease or obstructive sleep apnea, which may develop pulmonary hypertension and right ventricular dysfunction. Moreover, we did not evaluate the right ventricle function by echocardiography. Finally, the sample size was relatively small, and thus, more prospective studies with larger samples are required to verify our findings.

5.2. Conclusions

This study demonstrated that TR severity was exacerbated after CRT implantation. Furthermore, patients with moderate-to-severe TR had significantly less clinical and echocardiographic response to CRT when compared with patients with no or mild TR. Nevertheless, aggravation of TR following CRT implantation had no significant negative effect on the clinical and echocardiographic response to CRT. Therefore, it should not be considered a criterion for decision-making about CRT implantation other than acceptable criteria.

Acknowledgments

This study was supported by Tehran Heart Center, Tehran University of Medical Sciences, and Ahvaz Jundishapur University of Medical Sciences.

Footnotes

Authors' Contribution: Study concept and design: Babak Payami, Elham Mohammadyari; acquisition of data: Shahla Majidi, Arezou Zoroufian; analysis and interpretation of data: Elham Mohammadyari; drafting of manuscript: Babak Payami, Elham Mohammadyari; statistical analysis: Elham Mohammadyari; study supervision: Babak Payami, Shahla Majidi, Arezou Zoroufian; critical revision of the manuscript for important intellectual content: Babak Payami.

Conflict of Interests: The authors have no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to compliance with the confidentiality of the patients' information.

Ethical Approval: The study protocol was approved by the Institutional Committee of Medical Ethics and the Research Board of both universities (IR.AJUMS.REC.1392.115).

Funding/Support: Funding and research was supported by Ahvaz Jundishapur University of Medical Sciences and Tehran University of Medical Sciences. The authors had no personal financial interest in the research (Tracking Code: 92652).

Informed Consent: The participants provided written informed consent before enrolment.

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