Comparison of Outcomes in Patients With Heart Failure With Versus Without Lead-Induced Tricuspid Regurgitation After Cardiac Implantable Electronic Devices Implantations

Yoshihiro Seo, MD[a,*], Hideki Nakajima, PhD[b], Tomoko Ishizu, MD[c], Noriko Iida, PhD[b], Kimi Sato, MD[c], Masayoshi Yamamoto, MD[c], Tomoko Machino-Ohtsuka, MD[c], Akihiko Nogami, MD[c], Nobuyuki Ohte, MD[a], and Masaki Ieda, MD[c]

Cardiac implantable electronic devices (CIED) implantations may cause lead-induced tricuspid regurgitation (LITR). Although patients with CIED have the risk of functional non-lead induced TR (Non-LITR). This study aimed to compare of clinical outcome between LITR and Non-LITR. The mechanism of TR was determined by 3-dimensional echocardiography. The primary end point was heart failure (HF) hospitalizations after CIED implantation. In patients with HF events, subsequent clinical outcomes after HF hospitalization were compared between no TR, LITR, and Non-LITR groups. In eligible 373 patients, 67 patients had HF hospitalization, of whom worsened TR was observed in 49 patients. In the remaining 307 patients, worsened TR was observed in only 10 patients (3.3%). Of the 49 patients with worsened TR, 18 patients (37%) had LITR. In 67 patients with HF hospitalization, 25 patients (37%) met rehospitalization. All severe LITR persisted after HF events. Meanwhile, severe Non-LITR improved to moderate or mild level. Cox proportional hazard model analyses revealed LITR was the independent risk factor of rehospitalization. Both LITR and Non-LITR were common at HF events after CIED implantations. However, LITR persisted and might contribute to a worse prognosis. In patients with TR after CIED implantations, 3-dimensional echocardiography should be performed to diagnose the LITR accurately, which may contribute to improving the clinical outcome. **(Am J Cardiol 2020;130:85−93)**

Functional tricuspid regurgitation (TR) caused by remodeling of the tricuspid valve (TV) accompanied by right ventricular (RV) and right atrial remodeling is the most common cause of significant TR in patients with cardiac diseases.[1−3] In contrast, the number of patients who have received cardiac implantable electronic devices (CIED) including a permanent pacemaker (PM), implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT) device has been increased in patients with advanced cardiac diseases. As a result, lead-induced TR (LITR), which is caused by TV leaflet obstruction due to impingement by the CIED lead, has been noticeable.[4−9] In the background, development of 3-dimensional echocardiography (3DE) has played a critical role to identify the etiology of TR after CIED implantation.[8−11] As previous studies reported, significant TR after CIED implantation contributes to the poor clinical outcome.[6,7] Meanwhile, patients referred for CIEDs also have a high risk of heart failure (HF) with functional TR.[12] Therefore, TR after CIED implantation may be functional TR alone or mixture with a LITR. We hypothesized that LITR and functional TR may differently affect clinical outcomes in patients with CIED implantation. Then, the purpose of this study was to investigate the impact of LITR on clinical outcomes as compared with non-lead induced TR (Non-LITR).

Methods

Retrospectively, patients who were followed after CIED implantation from April 2011 to May 2017 at the University of Tsukuba hospital were enrolled. Patients who had moderate or more TR before CIED implantation were excluded. The hospital ethics committee approved the research protocol, and we provided information about this study online to allow patients to opt out (http://www.md.tsukuba.ac.jp/clinical-med/cardiology/research_group/research_group07.html).

First, we compared the baseline and follow-up echocardiographic data between patients with hospitalization due to decompensated HF after CIED implantation and those without HF events. In patients with moderate to severe TR after CIED implantation, TV was assessed by 3DE to identify the etiology of TR. In patients with HF hospitalization, data at HF admission were used to assess cardiac function and morphology. In the patients without HF events,

[a]Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [b]Clinical Laboratory, University of Tsukuba Hospital, Tsukuba, Japan; and [c]Department of Cardiology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan. Manuscript received March 10, 2020; revised manuscript received and accepted May 29, 2020.

Funding sources: None

Declarations of interest: None

*Corresponding author: Tel: +81- 52-853-8221, Fax: +81- 52-852-3796.

E-mail address: yo-seo@med.nagoya-cu.ac.jp (Y. Seo).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.05.039

echocardiographic data from at least 6 months after CIED implantation were used.

Second, subsequent clinical courses after HF hospitalization were compared between no worsened TR, Non-LITR, and LITR groups for 24 months after discharge. In this cohort, the primary end point was a composite of all-cause death and unplanned rehospitalization due to exacerbated HF. Also, changes in TR grades were reevaluated at ≥6 months after discharge from the first HF hospitalization after CIED implantation.

The 2-dimensional echocardiographic examinations were performed with a Vivid E9 system (GE Healthcare, Horten, Norway) equipped with an M5S transducer. Comprehensive echocardiographic studies for both the left and right sides of the heart were performed according to established guidelines.[13,14] Left ventricular ejection fraction (LVEF) was measured using the bi-plane disk summation method. Early diastolic mitral inflow velocity (E) was measured using the pulsed-wave Doppler method by placing the sample volume at the level of the mitral valve leaflet tips. The tissue Doppler-derived early diastolic mitral annular velocities were measured from the septal and lateral wall corner of the mitral annulus in the apical 4-chamber view. The ratio of E to the average peak early mitral annular velocities (e′) was calculated as an E/e′. The degree of tricuspid regurgitation (TR) was assessed by the vena contracta width of the TR jet (TR-VC). The TR-VC from the apical 4-chamber and RV inflow parasternal views were categorized as follows: <3 mm, mild TR; and 3 mm to 7 mm, moderate TR, and ≥7 mm, severe TR. Fractional area change of right ventricle (FAC) was calculated by tracking the RV end-diastolic area (RVDA) and end-systolic area (RVSA) in the apical 4-chamber view using the following formula: $(\mathrm{RVDA} - \mathrm{RVSA}) / \mathrm{RVDA} \times 100$. Tethering height was measured as the perpendicular from the line connecting the septal and lateral annulus to the coaptation point in the apical 4-chamber view. The TR pressure gradient (TRPG) was measured from peak TR velocity using the simplified Bernoulli equation. RA pressure (RAP) was estimated the diameter of the inferior vena cava (IVC) in the subcostal view with the patient in the supine position at 1.0 to 2.0 cm from the junction with the right atrium using the long-axis view. An IVC with a diameter <2.1 cm collapses >50% with a normal RAP of 3 mmHg, whereas an IVC with a diameter ≥ 2.1 cm collapses <50% with a high RAP of 15 mmHg. In scenarios in which IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg was selected. RV base diameter was measured as the maximal transversal dimension in the basal one-third of RV inflow. Worsened TR was defined as moderate or severe TR that was newly developed or worsened from trivial or mild TR compared with baseline.

The 3-dimensional echocardiography (3DE) examinations were performed with a Vivid E9 or E95 system (GE Healthcare) equipped with a 3V 3D transducer. Pyramidal, full-volume, real-time, 3D datasets were acquired over 6 consecutive cardiac cycles during breath holding in the RV inflow, short-axis, and apical 4-chamber views. All 3DE images were obtained at a 20−45 volume rate. The crop function was used to select an elevational cutting plane from the RV apex to the RV base or from the RA to the RV base to allow the visualization of all 3 leaflets of the TV during 1 cardiac cycle. As shown in Figure 1, in patients with worsened TR, a device lead position through a commissure of the TV was determined to be Non-LITR. Meanwhile, a device lead positioned on a leaflet that obstructed the closing was determined as LITR.

Results are expressed as n (%), mean ± standard deviation (SD), or median (interquartile range) where appropriate. Comparisons between 2 groups were made using Student's *t* test for continuous variables and Mann-Whitney's U test, and the chi-square test for categorical variables. One-way ANOVA with the post hoc Tukey−Kramer test was used for comparisons among 3 groups. The risk of clinical end points was determined with Cox proportional hazard models. Kaplan−Meier analysis was performed to

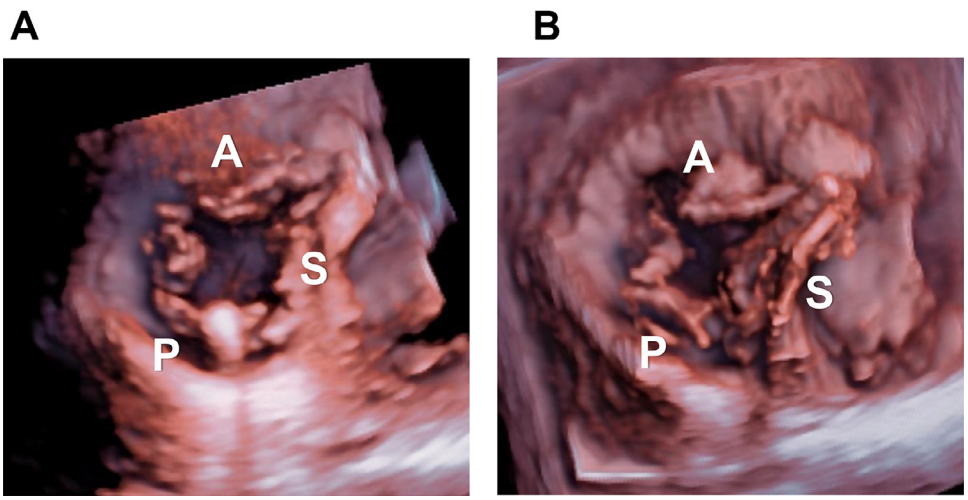

Figure 1. The 3-dimensional echocardiographic image of tricuspid valve from the right ventricular apex side. (*A*) lead-induced obstruction to tricuspid valve; the device lead (white arrow) is positioned on the posterior leaflet (P) that obstructed the closing. (*B*) non lead-induced obstruction to tricuspid valve; the device lead is positioned through the commissure between septal leaflet (S) and anterior leaflet (A).

determine the influence of TR type on the end points. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS was used (version 25.0, SPSS Inc., Chicago, IL, USA).

Results

Finally, 373 patients were studied among 379 patients with CIED implantation who were followed in the University of Tsukuba Hospital. The excluded 4 patients had moderate or severe TR at baseline, and the remaining 2 patients had inadequate echocardiographic images to determine the cause of worsened TR.

During a follow-up period of 6 to 24 months (median: 11 months), 67 (18%) patients hospitalized due to HF (Table 1). As compared with patients without HF events, the HF events group had significantly lower systolic pressure at baseline, the higher prevalence of NYHA class III or IV at baseline, more CRT, the higher prevalence of non-ischemic cardiomyopathy, previous ventricular tachycardia, and chronic atrial fibrillation, and higher use rate of each drug for HF. In addition, LVEF and FAC at baseline were significantly reduced in the HF events group.

In the HF events group, a worsened TR at HF hospitalization was observed in 39 (58.2%) patients. In contrast, in 307 patients without HF events during 24 months after device implantations, worsened TR was observed in only 10 patients (3.3%) at follow-up echocardiographic examinations. Of the combined 49 patients with worsened TR after CIED implantation, 18 patients (37%) had LITR, all of whom were hospitalized due to HF.

Comparisons between no worsened TR, Non-LITR, and LITR groups are summarized in Table 2. In addition, laboratory data and echocardiographic findings were compared between baseline studies and those at HF events or follow-up studies in patients without HF events. Patients with NYHA class III or IV at baseline and those with CRT were more prevalent in the LITR group, and those with CAF were more prevalent in the Non-LITR group compared with other groups. BNP levels in the LITR group were

Table 1
Comparisons of baseline clinical characteristics

Characteristic	HF events (0) (n = 306)	HF events (+) (n = 67)	p value
Age at baseline (year)	64.6 ± 13.7	61.6± 15.7	0.15
Men	195 (64%)	49 (73%)	0.21
Body mass index (kg/m^2)	23.1 ± 4.3	22.0 ± 3.5	0.054
Systolic blood pressure (mmHg)	119.3 ± 18.4	110.2 ± 18.7	<0.001
Heart rate, beats/min	67.4 ± 9.5	69.2 ± 11.9	0.23
NYHA class III or IV at baseline	104 (34%)	38 (57%)	0.001
Device			0.01
Cardiac resynchronization therapy	93 (30%)	33 (49%)	
Pacemaker	115 (38%)	17 (25%)	
Implantable Cardioverter Defibrillator	99 (32%)	17 (25%)	
Cardiac diseases			
Non-ischemic cardiomyopathies	101 (33%)	31 (46%)	0.04
Hypertrophic cardiomyopathy	35 (11%)	5 (8%)	0.35
Ischemic heart disease	43 (14%)	11 (16%)	0.61
Sick sinus syndrome	107 (35%)	11 (16%)	0.003
Advanced atrioventricular block	44 (14%)	1 (1.5%)	0.003
Ventricular tachycardia	50 (16%)	21 (31%)	0.01
Chronic atrial fibrillation	46 (15%)	17 (25%)	0.04
Paroxysmal atrial fibrillation	59 (19%)	7 (10%)	0.09
Laboratory data			
Hemoglobin (g/dl)	13.5 ± 1.7	12.9 ± 1.8	0.01
Estimated glomerular filtration rate (ml/min /1.73 m^2)	67.7 ± 22.7	66.2 ± 20.8	0.61
Brain natriuretic peptide (pg/ml)	93.1(38.8, 228.2)	185.2 (83.9, 580.3)	<0.001
Echocardiographic data			
Left ventricular ejection fraction (%)	52.8 ± 16.3	45.3 ± 17.5	0.002
E/e'	11.5 ± 5.8	12.8 ± 5.9	0.11
Fraction of right ventricular area change (%)	37.9 ± 5.7	35.4 ± 7.6	0.002
Pressure gradient of tricuspid regurgitation (mmHg)	21.8 ± 7.5*	23.6 ± 8.6	0.15
Right atrial pressure (mmHg)	3.6 ± 2.4	3.8 ± 2.4	0.61
Medications at baseline			
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker	118 (39%)	37 (55%)	0.01
β-blocker	173 (57%)	50 (75%)	0.006
Loop diuretics	175 (57%)	58 (87%)	<0.001
Spironolactone	53 (18%)	22 (33%)	0.006

Values are means ± SD or numbers (%), or median (interquartile range).
* Data was available in 289 patients.
E/E' = ratio of early diastolic peak velocity of transmitral flow to early diastolic mitral annular velocity.

Table 2
Comparisons of clinical and echocardiographic data

Variable	No worsened TR (n = 324)	Lead-induced TR (n = 18)	Non-lead-induced TR (n = 31)	p Value
Age (years)	63.9 ± 14.0	60.1 ± 13.4	66.1 ± 16.3	0.36
Men	214 (66%)	13 (72%)	17 (55%)	0.38
Body mass index (kg/m^2)	23.1 ± 4.3	21.9 ± 3.6	22.0 ± 3.0	0.20
Systolic blood pressure (mmHg)	118.8 ± 18.4	103.2 ± 15.6※	113.4 ± 18.9	0.001
Heart rate, beats/min	67.3 ± 9.7	68.7 ± 12.4	70.6 ± 11.6	0.20
NYHA class III or IV at baseline	114 (35%)	15 (83%)	13 (42%)	<0.001
Device				
Cardiac resynchronization therapy	105 (32%)	12 (67%)	9 (30%)	0.009
Pacemaker	115 (35%)	3 (17%)	15 (50%)	0.08
Implantable Cardioverter Defibrillator	105 (32%)	3 (17%)	7 (23%)	0.2
Cardiac diseases				
Non-ischemic cardiomyopathies	113 (35%)	9 (50%)	10 (32%)	0.37
Hypertrophic cardiomyopathy	34 (11%)	1 (5.6%)	5 (16%)	0.48
Ischemic heart disease	47 (15%)	2 (11%)	5 (16%)	0.89
Sick sinus syndrome	106 (33%)	2 (11%)	10 (32%)	0.16
Advanced atrioventricular block	44 (14%)	0 (-)	1 (3.2%)	0.07
Ventricular tachycardia	46 (14%)	9 (50%)	16 (51%)	<0.001
Chronic atrial fibrillation	45 (14%)	5 (28%)	13 (43%)	<0.001
Paroxysmal atrial fibrillation	61 (19%)	3 (17%)	2 (6.5%)	0.22
Medications at baseline				
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker	127 (39%)	14 (78%)	14 (45%)	0.004
β-blocker	189 (56%)	17 (94%)	15 (48%)	0.004
Loop diuretics	199 (61%)	17 (94%)	17 (55%)	0.01
Spironolactone	61 (19%)	6 (33%)	8 (25%)	0.22
Laboratory data				
Hemoglobin (1) (g/dl)	13.5 ± 1.7	12.5 ± 1.4	13.3 ± 2.1	0.05
Hemoglobin (2) (g/dl)	13.5 ± 1.4	12.4 ± 1.7※	13.3 ± 2.0	0.02
p value (1) versus (2)	0.74	0.83	1.0	
Estimated glomerular filtration rate (1) (ml/min /1.73 m^2)	67.7 ± 21.4	64.0 ± 23.1	66.5 ± 30.0	0.77
Estimated glomerular filtration rate (2) (ml/min /1.73 m^2)	64.0 ± 22.1	57.8 ± 35.2	58.1 ± 20.8	0.31
p value (1) versus (2)	<0.001	0.05	0.06	
Brain natriuretic peptide (1) (pg/ml)	91.0(40.0, 228.1)	428.5(148.3, 831.2) †	183.6(92.4, 345.6)	<0.001
Brain natriuretic peptide (2) (pg/ml)	67.6(32.0, 179.1)	517.5(83.6, 1175.0)†	170.0(104.9, 747.0)	<0.001
p value (1) versus (2)	<0.001	0.71	0.34	
Tricuspid regurgitation grade at follow-up Non / mild / moderate / severe	10 / 315 / 0 / 0	0 / 0 / 0 / 18	0 / 0 / 17 /14	<0.001
Left ventricular ejection fraction (1) (%)	52.1 ± 16.3	44.3 ± 19.9	50.1 ± 18.6	0.14
Left ventricular ejection fraction (2) (%)	52.4 ± 15.4	39.0 ± 19.6※	49.5 ± 19.5	0.002
p value (1) versus (2)	0.45	0.04	0.79	
E/E' (1)	11.7 ± 5.7	11.2 ± 5.9	12.8 ± 6.6	0.57
E/E' (2)	11.6 ± 5.2	13.2 ± 6.6	13.6 ± 7.0	0.07
p value (1) versus (2)	0.75	0.22	0.49	
Vena contracta width of tricuspid regurgitation (1) (mm)	1.8 ± 0.8	2.6 ± 0.8※	2.2 ± 0.3※	<0.001
Vena contracta width of tricuspid regurgitation (2), (mm)	1.9 ± 1.2	9.0 ± 2.1†	6.1 ± 2.5※	<0.001
p value (1) versus (2)	0.09	<0.001	<0.001	
Pressure gradient of tricuspid regurgitation (1) (mmHg)	21.9 ± 7.5	24.8 ± 11.3	23.7 ± 7.6	0.18
Pressure gradient of tricuspid regurgitation (2) (mmHg)	22.3 ± 6.8	26.1 ± 12.4#	30.7 ± 9.7※	0.01
p value (1) versus (2)	0.25	0.38	0.001	
Right atrial pressure (1) (mmHg)	3.5 ± 2.2	5.4 ± 4.1※	4.1 ± 3.1#	0.004
Right atrial pressure (2) (mmHg)	3.3 ± 1.5	10.9 ± 4.4†	6.0 ± 4.8※	<0.001
p value (1) versus (2)	0.01	<0.001	0.02	
Right ventricular base diameter (1) (mm)	29.6 ± 5.5	34.8 ± 6.4※	32.1 ± 4.4#	<0.001
Right ventricular base diameter (2) (mm)	29.4 ± 4.6	36.9 ± 5.8※,‡	33.7 ± 5.5※	<0.001
p value (1) versus (2)	0.32	0.07	0.09	

(*continued*)

Table 2 (***Continued***)

Variable	No worsened TR (n = 324)	Lead-induced TR (n = 18)	Non-lead-induced TR (n = 31)	p Value
Fraction of right ventricular area change (1) (%)	37.9 ± 5.7	33.2 ± 8.8※,‡	35.7 ± 6.7	0.001
Fraction of right ventricular area change (2) (%)	38.3 ± 4.7	31.4 ± 7.4※,‡	33.1 ± 6.8#	<0.001
p value (1) versus (2)	0.21	0.45	0.14	
Tethering height (1) (mm)	5.1 ± 1.7	7.9 ± 1.5†	6.2 ± 1.2※	<0.001
Tethering height (2) (mm)	5.2 ± 2.2	11.2 ± 1.8†	8.5 ± 2.9※	<0.001
p value (1) versus (2)	0.12	<0.001	<0.001	

Values are means ± SD or numbers (%), or median (interquartile range). (1) means data at baseline, and (2) means data at follow up in No worsened tricuspid regurgitation (TR) group and rehospitalization due to decompensated heart failure in Lead-induced TR and Non-lead-induced TR groups, respectively. E/E' = ratio of early diastolic peak velocity of transmitral flow to early diastolic mitral annular velocity.

※ $p < 0.01$ versus No worsened TR.

# $p < 0.05$ versus No worsened TR.

† $p < 0.01$ versus others.

‡ $p < 0.05$ versus Non-lead-induced TR.

significantly higher than in the other groups, both at baseline and follow-up. TR grade at follow-up was severe in all patients with LITR. In the Non-LITR group, 17 patients (55%) had moderate TR.

LVEF at follow-up in the LITR group was significantly reduced compared with that at baseline, and lower than those in other groups. TR-VC, RAP, RV base diameter, and tethering height were significantly larger in both worsened TR groups than that in the no worsened TR group even at baseline, and TR-VC, RAP, and tethering height significantly increased at follow-up studies. In the LITR group, RV dilatation progressed at hospitalizations. FAC in the LITR group was significantly lower than that in other groups even at baseline, and that in the Non-LITR group also was lower than that in the no worsened TR group at follow-up studies.

In 67 patients with HF hospitalization events after CIED implantation (Table 1), the clinical outcomes after discharge were assessed. During a follow-up period of 4 to 24 months (median: 19 months), 25 (37%) patients met rehospitalization. The comparisons between patients with and without rehospitalization are summarized in Table 3. Between them, 2 rehospitalized patients died due to malignant neoplasm.

Table 3
Comparisons between patients with rehospitalization and patients without rehospitalization after HF hospitalization events

Variable	Rehospitalization		p value
	No (n = 42)	Yes (n = 25)	
Age (years)	62.8 ± 14.9	58.2 ± 16.8	0.24
Men	29 (69%)	20 (80%)	0.32
NYHA class III or IV at discharge	27 (64%)	20 (80%)	0.17
Chronic atrial fibrillation	10 (24%)	7 (28%)	0.70
Cardiac resynchronization therapy	19 (45%)	14 (56%)	0.39
Pacemaker	14 (33%)	3 (12%)	0.08
Implantable Cardioverter Defibrillator	9 (21%)	8 (32%)	0.34
Clinical data at discharge of HF events			
Systolic blood pressure (mmHg)	116.5 ± 20.4	105.1 ± 10.7	0.02
Hemoglobin (g/dl)	13.1 ± 2.0	12.9 ± 1.6	0.59
Estimated glomerular filtration rate (ml/min /1.73 m^2)	58.7 ± 17.1	62.7 ± 31.3	0.50
Brain natriuretic peptide (pg/ml)	162.2 (73.6, 389.1)	742.2 (133.5, 1200)	0.01
Lead-induced tricuspid regurgitation	6 (14%)	12 (48%)	0.003
Non-lead-induced tricuspid regurgitation	14 (33%)	6 (24%)	0.42
Left ventricular ejection fraction (%)	46.2 ± 18.3	38.3 ± 19.7	0.10
E/e'	13.4 ± 6.1	14.9 ± 7.0	0.38
Fraction of right ventricular area change (%)	35.7 ± 7.1	30.7 ± 7.1	0.007
Right ventricular base (mm)	32.1 ± 5.5	36.4 ± 5.0	0.002
Tethering height (mm)	7.7 ± 2.8	11.0 ± 5.1	0.001
Vena contracta width of tricuspid regurgitation (mm)	4.7 ± 3.1	6.8 ± 3.4	0.01
Tricuspid regurgitation grade at hospitalization	16 / 17 /1 / 7	3 / 4 / 6 / 11	<0.001
Non / mild / moderate / severe			

Values are means ± SD or numbers (%), or median (interquartile range).

E/E' = ratio of early diastolic peak velocity of transmitral flow to early diastolic mitral annular velocity.

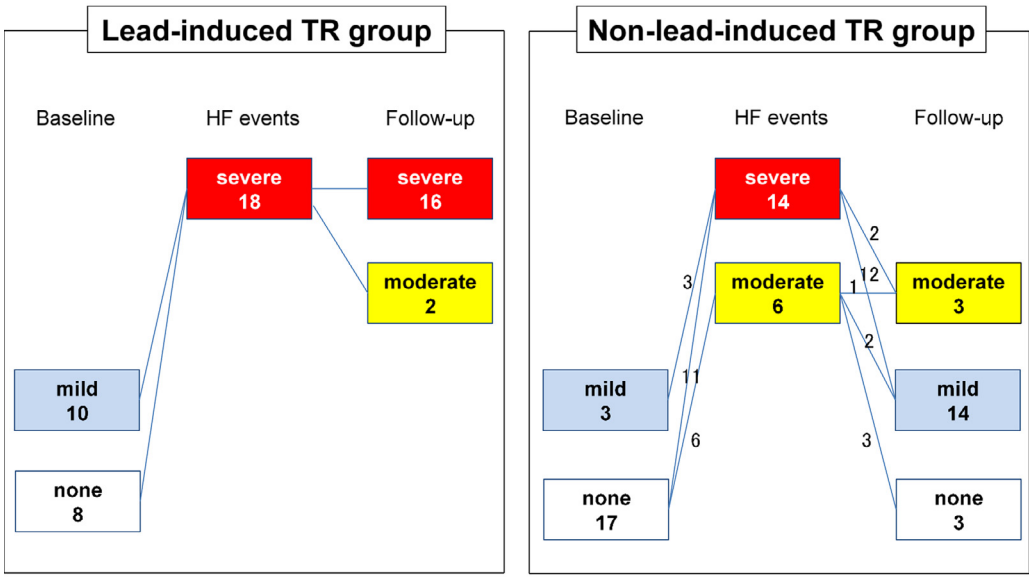

Figure 2. Sequential changes of tricuspid regurgitation grade. Comparison of changes of tricuspid regurgitation (TR) grades between the lead-induced TR group and the non-lead-induced TR group.

As compared with patients without rehospitalization, LITR was more prevalent in patients with rehospitalization. In the follow-up studies after the discharge of the first HF events, patients with rehospitalization showed more advanced RV and TV remodeling. In the rehospitalization group, 17 (68%) patients had moderate or severe TR. In contrast, moderate or severe TR was observed in only 8 (19%) patients in the group without rehospitalization.

The sequential changes of TR grade in patients with HF events were compared between LITR and Non-LITR groups (Figure 2). In 16 (89%) patients in the LITR group, worsened severe TR persisted during postdischarge follow-up. In contrast, in the Non-LITR group, worsened severe TR observed at HF events improved to mild level after discharge in 12 patients, and there were no patients with severe TR at follow-up.

The variables only, which had a significant association in a univariable Cox proportional hazard model analysis in variables in Table 3, were shown in Table 4. Due to the small number of patients reaching the end point, the multivariable analyses were performed with the LITR adjusted for $\log_{10}$BNP level and the other variable. As a result, Cox proportional hazard model analyses revealed the LITR was the independent risk factor of rehospitalization after adjusted by systolic blood pressure, $\log_{10}$BNP level and RV or TV echocardiographic parameters (Table 4). Figure 3 illustrates the cumulative event-free probability curves in the HF groups without worsened TR, the HF group with the LITR, and the HF group with the Non-LITR. A log-rank test revealed a statistically significant difference between the LITR group and the other 2 groups ($p = 0.002$ vs HF without worsened TR group, $p = 0.01$ vs. HF with the Non-LITR group). In the LITR group, 4 patients required lead removal and reindwelling, and 2 patients required tricuspid surgery.

Discussion

The major findings are as follows: (1) worsened TR was observed in more than a half of patients with HF events after CIED implantation, of which LITR was less than half but had severe grade in all cases; (2) all patients with LITR were hospitalized due to HF, which was observed more in patients with CRT; (3) LITR was associated with poor clinical outcomes after discharge of HF events compared with Non-LITR, and was selected as the independent risk factor of rehospitalization; and (4) the course of the TR grade was different for LITR and non-LITR, and the worsened LITR grade persisted during follow-up after the discharge of HF events.

In this study, 13% of patients among 373 patients exhibited worsened TR after CIED implantation, which is less than the results of 21.2% by Kim et al[4], 18.3% by Klutstein et al[5], and 38% by Höke et al[6] between patients with PPM or ICD implantation without CRT. The reasons for the differences are as follows; 1) First, TR grading depends on each study. In Klutstein's study, since visual assessments of TR grading were used, we cannot compare the results.[5] In Kim's study, significant TR grading was classified into 3.4% of mild-moderate TR, 12.8% of moderate TR, and 5.0% who developed moderate-severe or severe TR.[6] Perhaps, significant TR grade in our study may be more than moderate to severe level. And, in Höke's study, TR grade 3 and 4, which may be corresponding to our defined significant TR, was only 8%.[7] 2) Compared with our study, subjects were about 10 years older and in their 70s. Age has been identified as a risk factor of LITR.[4,6,7]

Although recent studies have focused attention on LITR in patients with CIED implantation,[4,9–11] the present study revealed that more than 60% of cases with worsened TR were not associated with impingement of CIED leads, which is believed to indicate functional TR.[15,16] Although

Table 4
Univariable and multivariable predictors of readmission by the Cox proportional hazard model

	Univariable			Multivariable Model1			Model 2			Model 3			Model 4			Model 5		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	pvalue	HR	95% CI	p value	HR	95% CI	p valve
Systolic blood pressure	0.97	0.95 – 0.99	0.04	0.99	0.97 – 1.02	0.56												
$Log_{10}BNP$	2.51	1.23 – 5.07	0.01	2.14	1.01 – 4.23	0.04	1.77	0.82 – 3.81	0.14	1.95	0.95 – 4.03	0.07	1.96	0.94 – 4.09	0.07	1.98	0.71 – 4.45	0.16
Lead-induced TR	3.65	1.65 – 8.07	0.001	2.82	1.19 – 6.70	0.01	2.83	1.23 – 6.50	0.01	2.71	1.21 – 6.36	0.01	2.94	1.32 – 6.56	0.008	2.01	1.03 – 4.29	0.04
Fraction of RV area change	0.94	0.89 - 0.98	0.006				0.97	0.92 – 1.02	0.21									
RV base	1.11	1.04 – 1.19	0.002							1.05	0.98 – 1.13	0.18						
Tethering height	1.07	1.02 – 1.13	0.008										1.06	0.98 – 1.13	0.11			
Vena contracta width	1.18	1.05 – 1.33	0.008													1.07	0.89 – 1.27	0. 49

BNP = brain natriuretic peptide; HR = hazard ratio; RV = right ventricular; TR = tricuspid regurgitation.

the progression of TV and RV remodeling after CIED implantation have been observed as the common processes of worsened TR, the differences of course of TR grades after HF rehospitalizations illustrate that the mechanisms of TR clearly differ between the LITR and the Non-LITR. First, given that the Non-LITR improved after HF rehospitalization, the Non-LITR is considered to be caused in the vicious cycle of congestive HF and maybe therefore reversible by HF treatments. In contrast, LITR itself might be the main factor in the onset of HF, because significant TR persisted during the clinical course after HF events. In this process, LITR could induce an irreversible vicious cycle of TR progression accompanied by TV and RV remodeling.

LITR was more prevalent in the rehospitalization group after HF events. The clinical impact of worsened TR after CIED implantation has been studied in longitudinal observational studies. Höke et al[6] reported that worsened TR after PM or ICD implantation is associated with worse long-term survival (hazard ratio [HR] = 1.687, p = 0.040) and/or more HF-related events (HR = 1.641, p = 0.019). Also, Delling et al.[7] reported that the presence of more than moderate to severe TR after PM implantation is associated with increased mortality (HR = 1.40, p = 0.027). However, the mechanism of worsened TR after CIED implantation did not be assessed in previous studies including these studies. In contrast, this study revealed the diagnosis of the cause of TR after CIED implantation to be critical because the prognosis depends on the etiology of TR.

What to emphasize is that the LITR cannot be controlled by HF medications and may be needed invasive interventions. As previously reported, 3DE is strongly recommended to assess mechanical interference of CIED leads for TV mobility and coaptation (8-11). The detailed assessments for the cause of TR after CIED implantation contribute to improving the clinical outcomes.

To preventing such a lead-induced TV dysfunction, leadless pacemakers may be optional therapy. However, a recent study reports that leadless pacemaker therapy caused worsened TR in 43% of the subjects through 12 months of follow-up.[17] The finding is an intersting result that defies expectations, although it needs to be confirmed in a larger survey. Also, the study revealed that mitral regurgitation and LV dysfunction were caused after leadless pacemaker therapy. RV pacing-induced LV dyssynchrony is believed as the main reason. Since the LITR was caused in many patients with CRT in this study, like RV lead pacing in such patients, RV leadless pacemaker therapy also is considered to have a limited indication.

Since this study is a retrospective, single-center study, we could not conclude the usefulness of 3DE to improve clinical outcomes through the prevention of LITR. In the future, the prospective studies in assessing the usefulness of 3DE guided CIED implantations are needed.

In conclusion, worsened TR caused by functional and lead-induced mechanical factors was common at HF events after CIED implantation. However, LITR persisted without responding to HF treatments and might contribute to a worse prognosis. Therefore, accurate diagnosis of LITR is critical to improving the clinical outcomes, and TV evaluations by 3DE may be helpful to determine the mechanism of worsened TR.

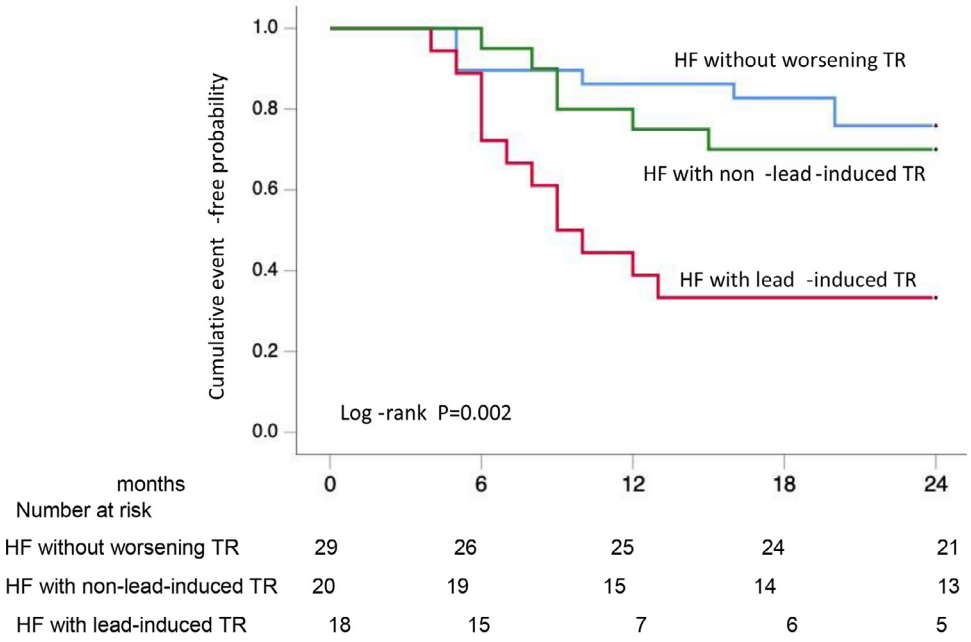

Figure 3. Kaplan−Meier survival curves based on the features of tricuspid regurgitation in heart failure hospitalization groups
HF: heart failure; TR: tricuspid regurgitation.

The contribution of each author is as fllows

Yoshihiro Seo: Conceptualization, Writing-Original Draft, Writing - Review & Editing, Visualization. *Hideki Nakajima*: Development or design of methodology; creation of models, Writing-Original Draft, Visualization. *Tomoko Ishizu, Noriko Iida, Kimi Sato, Masayoshi Yamamoto, Tomoko Machino-Ohtsuka*: Investigation and Formal analysis. *Akihiko Nogami, Nobuyuki Ohte and Masaki Ieda*: Supervision and Project administration

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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