Part 1

Heart Failure as a Complication of Pacemaker Therapy

Chapter 2

Significant Lead-induced Tricuspid Regurgitation is Associated with Poor Prognosis at Long Term Follow-up

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Heart. 2014 Jun;100(12):960-8

Trivial tricuspid regurgitation (TR) is a common echocardiographic finding in healthy individuals.[46] However, significant TR (grade ≥2) has been demonstrated to be associated with poor prognosis, regardless of the underlying cardiac pathology.[47] Significant TR can be a primary valvular disease (due to valve lesion) or secondary to tricuspid annular dilatation and/or right ventricular (RV) remodeling. In addition, placement of a RV (trans-tricuspid) lead has also been associated with a higher risk of TR. However, the incidence of lead-induced TR, time course and effects on long-term outcome remain unknown.[48-53] Previous studies have reported the incidence of TR immediately after implantation, focusing on the potential mechanisms of valve dysfunction (perforation, impingement, adherence to the leaflets).[49,54] However, data on the long-term incidence of TR after device implantation and, more importantly, data on the impact of significant TR on cardiac performance and clinical outcome are still lacking. Expanding indications for device therapy and aging of the population, with growing numbers of implanted pacemakers (PM) and cardioverter-defibrillators (ICD), may result in increased incidence of lead-induced TR with important clinical consequences in the near future.[55-58] Therefore, the objective of this evaluation was first to assess the incidence of significant lead-induced TR at long-term follow-up. In addition, the impact of significant lead-induced TR on cardiac performance and on long-term prognosis was evaluated.

METHODS

Patients

Patients undergoing an ICD or PM implantation at the Leiden University Medical Center between January 2002 and June 2009 were included in the present analysis. Data on baseline patient characteristics, implantation procedure, device characteristics and settings, and all follow-up visits were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Indication for device implantation based on international guidelines was primary and secondary prevention of sudden cardiac death in ICD recipients, and sick sinus syndrome and advanced degree atrioventricular (AV) block in PM recipients.[58] Due to evolving guidelines, particularly on prevention of sudden cardiac death, eligibility for device implantation in this population might have changed over time, based on the results of landmark clinical trials.[58-60]

Patients with de novo implantation of pacing devices were included. Exclusion criteria were: 1) previous transvenous (temporary) cardiac pacing system implantation, cardiac valve surgery, congenital heart disease or organic TR, in order to exclude

other causes of TR prior to device implantation; 2) absence of an echocardiographic evaluation within 6 months before device implantation, in order to allow appropriate comparison between pre and post-implantation evaluations; 3) presence of an echocardiographic evaluation only in the first 6 months after the procedure (evaluation mainly in relation with procedure-related complications) or only more than 1.5 year after implantation (evaluation mainly driven by a new clinical event), in order to avoid selection bias; 4) occurrence of heart failure hospitalization or other major cardiac events in the period between the 2 echocardiographic evaluations, in order to exclude potential confounding factors in the comparison of TR before and after device implantation; 5) upgrades of systems to CRT (with or without ICD capabilities) to avoid the potential beneficial effect of resynchronization on cardiac performance. To evaluate whether lead placement might have induced significant TR and in order to ensure enough time for potential lead-related structural or functional changes to occur, only patients with a follow-up echocardiographic evaluation within 1-1.5 year after the implantation (according to standard follow-up visits) and with a minimal follow-up of 1 year after the echocardiographic evaluation were included.

Device implantation, settings and interrogations

All pacing and defibrillator systems were transvenously implanted and in all patients the RV lead was implanted in the RV apex. The PM settings were individually tailored based on the indication for cardiac stimulation. All patients were followed up every 3–6 months after implantation and devices were interrogated at the implanting centre. For the evaluation of the potential confounding effect of pacing on outcome, the last percentage of pacing prior to the follow-up echocardiography was used.

Echocardiographic evaluation

Echocardiographic assessment was performed with patients in the left lateral decubitus position, using a commercially available system (Vivid 7 and E9, GE-Vingmed Ultrasound, Horton, Norway). Standard 2-dimensional and Doppler images were recorded and saved in cine-loop format for off-line analysis (EchoPac, version 110.0.0, GE-Vingmed, Horton, Norway). Echocardiographic evaluation was performed according to the most recent recommendations and included quantification of LV end-diastolic and end-systolic volumes and of LV ejection fraction (LVEF) by biplane Simpson's method.[61,62] LV diastolic function was evaluated according to current recommendations, using transmitral flow Doppler velocities and tissue Doppler imaging-derived mitral annular velocities.[63] Transmitral early (E) and late (A) diastolic velocities and the E-wave deceleration time were measured using the pulsed-wave Doppler recordings at the apical four-chamber view with a 2-mm sample volume at the tips of the mitral leaflets. Using tissue Doppler imaging, the

peak early diastolic myocardial velocities at septal and lateral borders of the mitral annulus were measured and averaged to calculate the mean early diastolic myocardial velocities (E'). The E/E' ratio was therefore derived as a measure of LV filling pressures. Mitral regurgitation severity was graded according to a multiparametric approach as recommended.[61] In addition, left atrial volume was measured using the Simpson's method and indexed to body surface area. Furthermore, RV dimension was assessed by tricuspid annular diameter and RV end-diastolic area, while RV function was quantified by RV fractional area change and tricuspid annular plane systolic excursion (TAPSE).[62,64] Right atrial (RA) diameter was also measured and RA pressure was estimated using the inferior vena cava size and collapsibility. Systolic pulmonary arterial pressure (sPAP) estimated as the sum of the RA pressure and the peak pressure gradient between RV and right atrium, as measured on the TR spectral continuous-wave Doppler signal.[64] TR severity was graded by multiparametric approach including the assessment of vena contracta width and regurgitant jet area by color Doppler, the evaluation of TR continuous-wave Doppler signal intensity and the pattern of the systolic blood flow in the hepatic veins.[61,64]

Definition of significant lead-induced TR

In order to evaluate the presence and impact of a significant lead-induced TR, patients with stable TR, improved TR or clinically irrelevant deterioration of TR (grade 0 or 1) at 1-1.5 year after implantation (no significant lead-induced TR) were compared with patients with significant TR increase at follow-up reaching a grade ≥2 (significant lead-induced TR).

Long-term follow-up and end points

Long-term follow-up was performed by chart review and telephone contact with the general practitioner. Survival data were obtained by reviewing medical records and retrieval of survival status through the municipal civil registries. The primary end point was all-cause mortality. The secondary end point was defined as the combined end point of all-cause mortality and heart failure related events: hospitalization for heart failure, surgical LV restoration, surgical tricuspid valvuloplasty or upgrade to cardiac resynchronization therapy (whichever comes first).

Statistical analysis

Variables are presented as mean values ± standard deviation when normally distributed, as median and interquartile range (IQR) when non-normally distributed, or as frequencies and percentages when variables were categorical or ordinal. Differences in baseline characteristics between the two groups were evaluated using the unpaired Student t-test (continuous variables) and $\chi 2$ (categorical data) and Wil-

coxon rank sum test (non-normally distributed continuous variables) as appropriate. Wilcoxon matched-pairs signed-rank test was used to test the significance change in the ordinal variables at follow-up. Differences in echocardiographic variables within and between the patient-groups were compared by repeated-measures ANOVA, including interaction between group and time. Generalized estimating equations (GEE) was used to compare changes in non-normally distributed echocardiographic parameters or ordinal echocardiographic parameters. Cumulative incidences with 95% confidence intervals (CI) of all-cause mortality and heart failure related events were analyzed using the method of Kaplan–Meier with log-rank tests for comparison between groups. The follow-up onset was set at the moment of the follow-up echocardiographic evaluation. In addition, in patients with LVEF <40% at baseline was a subgroup analysis performed to evaluate the impact of significant lead-induced TR on the primary and secondary end points. To assess whether significant lead-induced TR was associated with an increased mortality and/or heart failure related events, Cox proportional hazards modeling was used. Univariate analysis was performed among clinical and echocardiographic variables at the time of the follow-up echocardiography and subsequently, all variables with a p-value of <0.05 and no similarity to other parameters (concerning LV and RV dimension and function parameters), were included in the multivariable model. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed by using IBM PASW Statistics, version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients

A total of 239 patients (184 male, mean age 60±14 years, 191 ICD devices) were included in the present analysis. Clinical and echocardiographic characteristics of the patient population before implantation are summarized in Table 1. Indication for ICD was primary prevention in 119 (62%) patients, while indication for cardiac stimulation was sick sinus syndrome in 27 (56%) and AV block in 21 (44%) in PM patients.

Significant lead-induced TR

At baseline, some degree of TR (defined as grades I-II) was present in 153 patients (64%) patients and the distribution of TR grades in the whole patient population before (and after) lead implantation is summarized in Figure 1. A significant worsening of TR was observed after lead implantation in the whole population (Wilcoxon p<0.001) and in particular significant lead-induced TR was observed in 91 (38%) patients. Pre-implantation clinical and echocardiographic characteristics of patients

Table 1. Baseline clinical and echocardiographic characteristics of the patient population

	Overall (n=239)	No significant lead-induced TR (n=148)	Lead-induced significant TR (n=91)	p-value
Age, years	60±14	60±14	61±13	0.893
Male, n(%)	184(77)	114(77)	70(77)	0.985
Ischemic heart disease, n(%)	153(64)	96(65)	57(63)	0.728
QRS duration, ms	114±28	112±28	116±28	0.362
PM/ICD, n (%)	48(20) / 191(80)	29(20) / 119(80)	19(21) / 72(79)	0.810
PM indication: SSS/AV block, n(%)	27(56) / 21(44)†	16(55) / 13(45)†	11(58) / 8(42)†	0.955
ICD indication: primary prevention n(%)	119(62)*	78(66)*	41 (57)*	0.183
Percentage of pacing for PM, median [IQR]	100 [100-100]	100 [100-100]	100 [97-100]	0.065
Percentage of pacing for ICD, median [IQR]	0 [0-1]	0 [0-0]	0 [0-2]	0.149
Atrial fibrillation, n(%)	75(32)	40(27)	35(39)	0.056
Diabetes, n(%)	42(18)	29(20)	13(15)	0.308
NYHA functional class	2 [1-2]	2 [1-2]	2 [1-2]	0.727
LVEDV, ml	151±63	149±58	151±71	0.808
LVESV, ml	95±54	96±49	95±61	0.892
LVEF,%	39±14	38±14	40±13	0.356
E/A ratio	1.0 [0.7-1.4]	1.1 [0.8-1.6]	1.0 [0.7-1.4]	0.748
E-wave deceleration time, ms	225±74	217±73	238±75	0.053
Average E' (cm/s)	6.49±2.41	6.22±2.16	6.93±2.72	0.096
E/E' ratio	11 [8-15]	11 [8-15]	12 [8-16]	0.737
Mitral regurgitation grade ≥2**	62(29)	40(29)	22(27)	0.723
Left atrial volume (ml/m²)	36±7	36±7	37±8	0.443
RV end-diastolic area, mm²	16.1±5.0	16.5±5.1	15.3±4.8	0.074
RV fractional area change,%	39±12	38±13	41±11	0.082
TAPSE, mm	17.0±4	17.0±4.4	17.4±4.5	0.481
Right atrial diameter, cm	3.5±0.9	3.6±0.9	3.5±0.9	0.298
Tricuspid annular diameter, cm	3.6±0.8	3.6±0.8	3.6±0.8	0.931
sPAP, mmHg	33±12	32.9±12.0	33.0±11.0	0.916
Tricuspid regurgitation grade 0	81(33.9)	57(38.5)	24(26.4)	0.056
Tricuspid regurgitation grade 1	131(54.8)	71(48.0)	60(65.9)	
Tricuspid regurgitation grade 2	22(9.2)	16(10.8)	6(6.6)	
Tricuspid regurgitation grade 3	5(2.1)	4(2.7)	1(1.1)	

Values are mean±SD or median [interquartile range]. AV-block=atrioventricular block; GFR= glomerular filtration rate; ICD=implantable cardioverter defibrillator; IQR= interquartile range; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NYHA= New York heart association; PM=permanent pacemaker; RV=right ventricular; sPAP=systolic pulmonary arterial pressure; SSS=sick sinus syndrome; TAPSE=tricuspid annular plane systolic excursion. † among patients with PM, * among patients with ICD, ** MR grade was available in 217 patients.

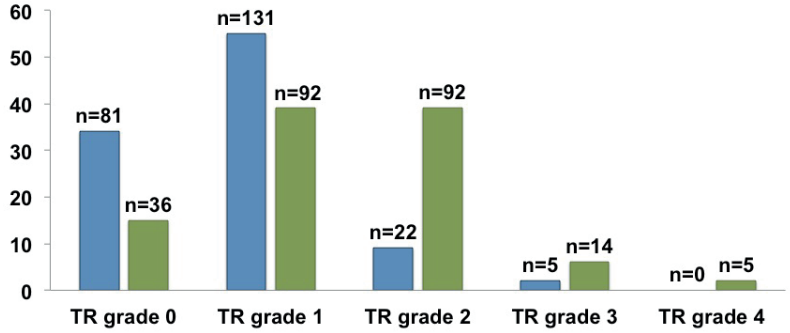

Figure 1. Distribution of tricuspid regurgitation (TR) grade in the study population before and after right ventricular (RV) lead implantation.

with significant lead-induced TR and no significant lead-induced TR were compared in Table 1. No significant differences were observed between the 2 groups, except for a trend (non-significant) of more frequent atrial fibrillation (AF), a higher prevalence of TR grade 1, and a higher RV fractional area change with a smaller RV end-diastolic area among patients with significant lead-induced TR.

Impact of significant lead-induced TR on cardiac performance

Echocardiographic changes after lead placement in patients with and without significant lead-induced TR are summarized in Table 2. Similar changes over time in LVEF and diastolic function severity were observed between the two groups (see interaction group and time p-value in Table 2). Similar changes over time in LVEF, diastolic function and in mitral regurgitation severity were observed between the two groups (see interaction group and time p-value in Table 2). Although no significant changes over time in RV function (TAPSE and RV fractional area change) were observed in both groups, RV size significantly increased over time only in patients with significant lead-induced TR. In addition, an enlargement of RA diameter was observed in this group of patients. Finally, pulmonary pressures increased over time only in patients with lead induced significant TR (from 33±11 to 41±15 mmHg versus 33±12 to 33±10 mmHg, see interaction group and time p-value in Table 2).

Impact of significant lead-induced TR on long-term prognosis

The relation between significant lead-induced TR and the primary (all-cause mortality) and secondary (all-cause mortality and heart failure related events) end points was evaluated over a median long-term follow-up of 58 months (IQR 35-76 months) after the repeated echocardiographic evaluation. During the follow-up period, a total of 62 deaths (26%) were observed. A higher all-cause mortality rate (primary end

Table 2. Changes in echocardiographic variables over time (from baseline to 1-1.5 year follow-up) in patients with and without significant lead-induced TR.

	No significant lead-induced TR (n=148)		Lead-induced significant TR (n=91)		p-value
Variables	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**interaction group and time**
LVEDV, ml	149±58	156±65	151±71	163±65*	0.507
LVESV, ml	96±49	103±59*	95±61	107±56*	0.441
LVEF,%	38±14	37±12	40±13	36±11*	0.064
E/A ratio	1.1 [0.8-1.6]	0.9 [0.7-1.4]	1.0 [0.7-1.4]	1.1 [0.6-1.9]	0.961
E-wave deceleration time, ms	217±73	234±72	238±75	238±87	0.227
Average E' (cm/s)	6.22±2.16	5.93±1.91	6.93±2.72	6.95±2.70	0.680
E/E' ratio	11 [8-15]	11 [8-19]	12 [8-16]	11 [8-18]	0.603
Mitral regurgitation grade 0 †	51(38)	44(32)	30(37)	27(33)	0.276
Mitral regurgitation grade 1	45(33)	48(35)	29(36)	30(37)	
Mitral regurgitation grade 2	31(23)	33(24)	16(20)	18(22)	
Mitral regurgitation grade 3	7(5)	10(7)	6(7)	6(7)	
Mitral regurgitation grade 4	2(2)	3(2)	-	1(1)	
Left atrial volume (ml/m²)	36±7	38±7	37±8	40±9	0.366
RV end-diastolic area, mm²	17±5	16±5	15±5	17±6*	**0.009**
RV fractional area change,%	38±13	37±11	41±11	37±13*	0.154
TAPSE, mm	17±4	16±4*	17±5	17±5	0.849
Right atrium diameter, mm	36±9	36±8	35±9	39±10*	<**0.001**
Tricuspid annular diameter, mm	36±8	36±8	36±8	39±9*	0.074
sPAP, mmHg	33±12	33±10	33±11	41±15*	<**0.001**

Values are mean±SD or median [interquartile range]. Bold p-values are statistically significant. LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; RV=right ventricular; sPAP=systolic pulmonary arterial pressure. *p<0.05, baseline vs. follow-up. † Mitral regurgitation grade was available in 217 patients at baseline and in 220 patients at follow-up.

point) was observed in patients with significant lead-induced TR (log rank p=0.038; Figure 2A). In the univariate Cox proportional hazard ratio (HR) analysis, significant lead-induced TR reached a HR of 1.687 (95%-CI: 1.023-2.780,p=0.040) (Table 3). After adjustment for the other clinical and echocardiographic characteristics, significant lead-induced TR was independently associated with survival (with adjusted HR of 1.749[95%-CI: 1.008-3.035], p=0.047) together with age, percentage of pacing and LVEF.

Similarly, as shown in Figure 2B, the secondary end point (combination of all-cause mortality and heart failure related events) was observed in 90 (38%) patients. The secondary end point was more frequent in lead-induced significant TR patients

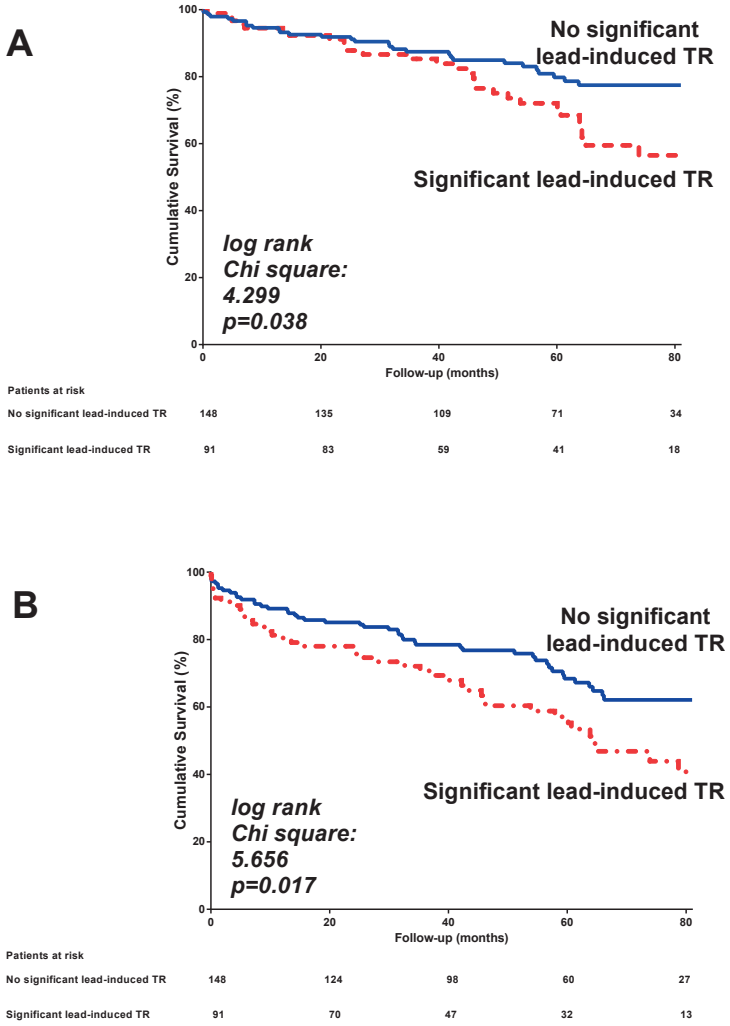

Figure 2. (A) Kaplan-Meier survival curves for the time to the primary end point (all-cause mortality) in patients with and without significant lead-induced TR with the follow-up onset at time of the follow-up echocardiography. **(B)** Kaplan-Meier survival curves for the time to the secondary end point (all-cause mortality and heart failure related events) in patients with and without significant lead-induced TR with the follow-up onset at time of the follow-up echocardiography

(log rank p=0.017). In the univariate analysis, significant lead-induced TR was associated with worse outcome with a HR of 1.641 (95%-CI: 1.087-2.480,p=0.019) (Table 4). In the multivariate model, significant lead-induced TR was independently associated with the occurrence of the secondary end point (adjusted HR of 1.649, 95%-CI: 1.043-2.599,p=0.032) together with age, LVEF and mitral regurgitation.

The subgroup analysis in patients with baseline LVEF<40% demonstrated that significant lead-induced TR was associated with poor survival free from the primary end point (HR 2.184 [95%-CI: 1.112-4.288], Figure 3A) but not with survival free from the secondary end point (HR 1.428 [95%-CI: 0.832-2.451], Figure 3B).

Table 3. Univariate and multivariate Cox regression survival analysis for the primary endpoint (all-cause mortality)

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**
Age, per year	1.079	1.048-1.112	<**0.001**	1.064	1.032-1.098	<**0.001**
Male sex	1.194	0.635-2.246	0.582			
Ischemic etiology	1.684	0.963-2.944	0.068			
Atrial fibrillation	1.373	0.823-2.290	0.224			
Diabetes	1.705	0.963-3.018	0.067			
ICD system(versus PM)	0.897	0.507-1.589	0.710			
Percentage of pacing, per %	1.007	1.002-1.013	**0.006**	1.008	1.002-1.015	**0.008**
LVEDV, per ml	1.005	1.002-1.009	**0.001**			
LVESV, per ml	1.007	1.004-1.011	<**0.001**			
LVEF, per %	0.968	0.946-0.990	**0.005**	0.973	0.947-0.999	**0.041**
Mitral regurgitation grade 0 (reference group)			**0.028**			0.510
Mitral regurgitation grade 1 (vs. reference group)	0.449	0.219-0.922		1.185	0.522-2.691	
Mitral regurgitation grade 2 (vs. reference group)	0.840	0.409-1.727		1.445	0.626-3.336	
Mitral regurgitation grade 3 (vs. reference group)	1.815	0.737-4.468		2.067	0.695-6.146	
Mitral regurgitation grade 4 (vs. reference group)	2.695	0.632-11.483		2.634	0.662-10.488	
RV end-diastolic area, per mm²	1.069	1.025-1.114	**0.002**			
RV fractional area change, per %	0.975	0.953-0.996	**0.022**			
TAPSE, per mm	0.914	0.856-0.976	**0.007**	0.974	0.910-1.042	0.447
Right atrial diameter, per mm	1.412	1.071-1.861	**0.014**			
Tricuspid annular diameter, per mm	1.748	1.325-2.306	<**0.001**			
sPAP, per mmHg	1.046	1.029-1.063	<**0.001**			
Significant lead-induced TR	1.687	1.023-2.780	**0.040**	1.749	1.008-3.035	**0.047**

Bold values are statistically significant. ICD=implantable cardioverter-defibrillators; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; RV=right ventricular; sPAP=systolic pulmonary arterial pressure; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation.

Bold values are statistically significant. ICD=implantable cardioverter-defibrillators; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; RV=right ventricular; sPAP=systolic pulmonary arterial pressure; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation.

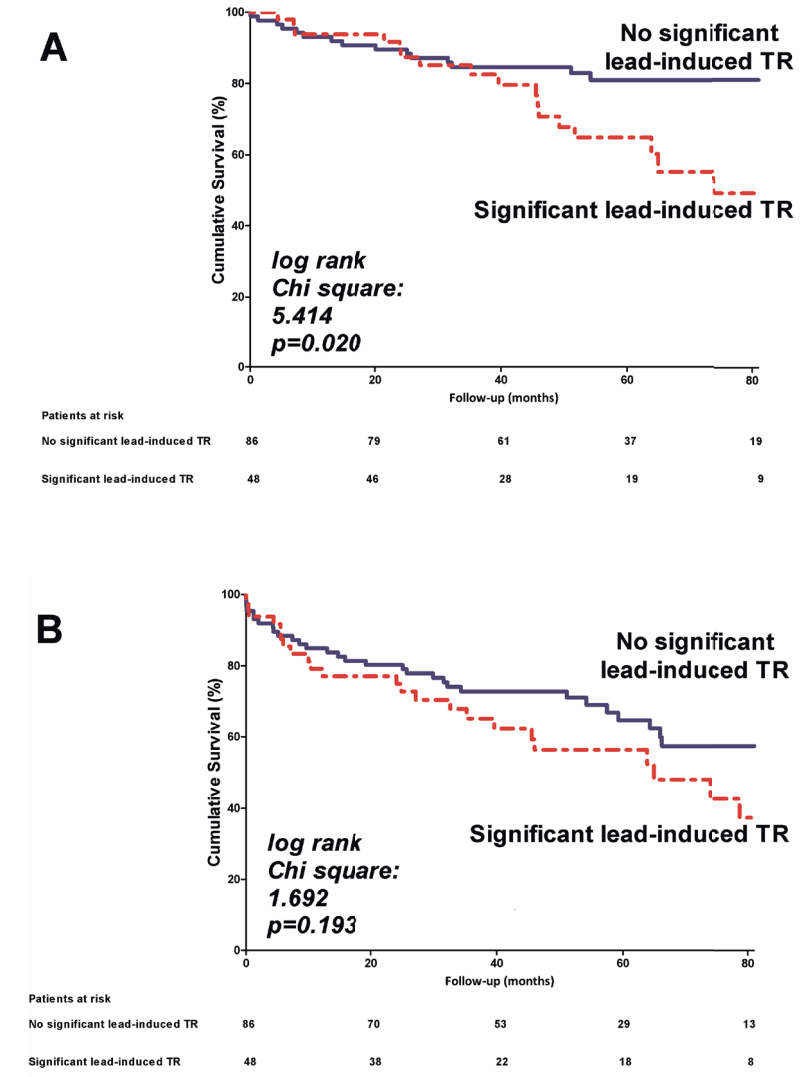

Figure 3. Subgroup analysis in patients with LVEF <40% before device implantation **(A)** Kaplan-Meier survival curves for the time to the primary end point (all-cause mortality) in patients with and without significant lead-induced TR with the follow-up onset at the second echocardiography. **(B)** Kaplan-Meier survival curves for the time to the secondary end point (all-cause mortality and heart failure related events) in patients with and without significant lead-induced TR with the follow-up onset at the second echocardiography.

Table 4. Univariate and multivariate Cox regression survival analysis for the secondary endpoint (all-cause mortality and heart failure related events)

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**
Age, per year	1.039	1.018-1.061	<**0.001**	1.026	1.003-1.050	**0.030**
Male sex	0.908	0.557-1.481	0.699			
Ischemic etiology	1.632	1.035-2.575	**0.035**	1.040	0.602-1.797	0.887
Atrial fibrillation	1.058	0.683-1.639	0.801			
Diabetes	1.277	0.777-2.098	0.335			
ICD device and lead	1.283	0.764-2.155	0.347			
Percentage of pacing, per %	1.003	0.999-1.008	0.157	1.001	0.996-1.007	0.636
LVEDV, per ml	1.006	1.003-1.008	<**0.001**			
LVESV, per ml	1.008	1.005-1.011	<**0.001**			
LVEF, per %	0.958	0.939-0.977	<**0.001**	0.971	0.949-0.994	**0.013**
Mitral regurgitation grade 0 (reference group)			**0.011**			**0.014**
Mitral regurgitation grade 1 (vs. ref. group)	0.511	0.277-0.943		1.175	0.618-2.235	
Mitral regu itation grade 2 ((vs. ref. group)	1.042	0.572-1.896		1.345	0.687-2.633	
Mitral regurgitation grade 3 (vs. ref. group)	2.371	1.081-5.201		2.659	1.126-6.276	
Mitral regurgitation grade 4 (vs. ref. group)	0.915	0.124-6.732		6.559	1.861-23.116	
RV end-diastolic area, per mm²	1.048	1.011-1.086	**0.010**			
RV fractional area change, per %	0.966	0.949-0.984	<**0.001**			
TAPSE, per mm	0.913	0.864-0.963	**0.001**	0.971	0.917-1.028	0.307
Right atrial diameter, per mm	1.355	1.082-1.699	**0.008**			
Tricuspid annular diameter, per mm	1.509	1.204-1.892	<**0.001**			
sPAP, per mmHg	1.059	1.042-1.075	<**0.001**			
Significant lead-induced TR	1.641	1.087-2.480	**0.019**	1.649	1.043-2.599	**0.032**

Bold values are statistically significant. ICD=implantable cardioverter-defibrillators; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; RV=right ventricular; sPAP=systolic pulmonary arterial pressure; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation

DISCUSSION

The main findings of the present study include: (1) significant lead-induced TR was observed in 38% of the patients 1-1.5 year after placement of an RV lead; (2) significant lead-induced TR was associated with significant RV and right atrium enlargement, and with increased pulmonary pressures at follow-up and; (3) significant lead-induced TR was independently associated with worse long-term clinical outcomes

(all-cause mortality alone or combined with heart failure related events) after device implantation.

Significant lead-induced TR

The presence of a lead through the tricuspid valve apparatus has been suggested as one of the mechanisms of TR. However, only few studies described the incidence of lead-induced TR acutely after implantation and no data are available from the large randomized clinical trials on cardiac devices.[48,50,51] Kim et al evaluated the presence of TR in 248 ICD or PM recipients shortly after implantation and found in 24% of the patients an increase of TR by >1 grade.[48] In addition, this increase in TR severity was more pronounced among patients with no or trivial TR, while patients with already grade 1-to-3 TR showed only modest worsening of TR. The current study, with longer term follow-up (1-1.5 years), reported higher incidence of significant (grade ≥2) TR progression (38%), suggesting the additional role over time of chronic lead and valvular structural and functional alterations. Similarly, we observed a trend toward a higher incidence of significant lead-induced TR among patients with only trivial TR before implantation as compared to patients with significant TR. In patients with significant TR before device implantation, with dilated tricuspid annulus and/or of leaflet malcoaptation the presence of RV lead may not have significant additional impact on TR severity. In contrast, in patients with new onset significant TR, a RV lead hampering proper leaflet coaptation seems to be an important pathophysiological factor.

However, the exact mechanism of development and progression of TR after cardiac device placement is not fully elucidated and may result from the mechanical interference of the RV lead with the tricuspid valve[48,49] and/or from a direct effect on TR of RV pacing.[65] In the current study, no significant differences were observed in baseline clinical, echocardiography and device-related (ICD versus PM) characteristics among patients who developed significant TR after implantation or not, underscoring the challenge of finding evident predisposing pre-implantation parameters associated with lead-induced TR. These results suggest that significant lead-induced TR may not result only from progression of a pre-existing cardiac/valvular disease but from the interaction between RV lead and tricuspid valve apparatus.

Impact of significant lead-induced TR on cardiac performance

The current study showed that patients with significant lead-induced TR at follow-up revealed an increase in RV and RA dimensions and an increase in pulmonary pressures, while these parameters remained unchanged in patients without significant lead-induced TR. RV function, as assessed by TAPSE and RV fractional area change, did not change significantly at follow-up in patients with significant lead-induced TR,

probably due to the facilitated ejection in a low-resistance chamber (from the RV to the right atrium).

The impairment of the RV performance observed in patients with significant lead-induced TR is unlikely to be secondary to a worsening of LV performance. The overall cohort showed in fact a slight worsening of LV size and function at follow-up, as probably expected according to the natural history of heart failure or RV chronic pacing. However, no significant differences were noted in the changes over time in LV volumes and systolic and diastolic function among patients with or without significant lead-induced TR (see p-value for interaction group and time). Furthermore, the change over time in severity of mitral regurgitation was also similar among patients with or without significant lead-induced TR.

A potential explanation for increased pulmonary pressures, and therefore progression of TR and RV dilatation, might be the occurrence of multiple subclinical pulmonary emboli secondary to RV lead thrombus formation. Supple et al. described a significantly higher increase in pulmonary pressure in patients with a mobile thrombus around the leads following cardiac device implantation as compared to patients without mobile thrombus.[66] However, the increase in pulmonary pressures did not reach the cut-off value proposed by current guidelines to define pulmonary hypertension (>50 mmHg) and therefore the diagnosis of pulmonary hypertension is not definitive in the absence of other echocardiographic parameters.[63] This suggests that the development of significant TR after lead implantation plays a primary role and is one of the major determinants of the changes in RV performance.

Impact of significant lead-induced TR on long-term prognosis

Although the presence of significant TR, regardless of etiology, is a well-known prognostic factor, data on long-term outcome in patients with significant TR after RV lead implantation have not been reported.[47] The present study demonstrated the independent association between significant lead-induced TR and all-cause mortality (combined with heart failure related events or not). Other variables independently associated with the long-term outcomes (primary and secondary) were age, LVEF, percentage of RV pacing and significant mitral regurgitation, which are all known determinants of development of heart failure and increased mortality. Particularly, the subanalysis according to the baseline LVEF showed that significant lead-induced TR in patients with depressed LVEF (<40%) at baseline was associated with poor prognosis. RV pacing has been previously shown to be associated with an increased risk of LV (progressive) dysfunction and heart failure events.[67-69] This detrimental effect of RV pacing might be mediated by induction of LV dyssynchrony[69,70] but also by a direct negative effect on the severity of TR, as suggested by Vaturi et al.[65] However, analyses of large trials showed that implantation of an ICD, even with minimal

percentage of RV pacing, was associated with an increased risk of congestive heart failure hospitalizations and death as compared to controls.[71] The exact reason for this increased risk of heart failure events was not so far elucidated but, considering the results of the current study, might also be explained by lead-induced TR. In fact, even modest grades of TR were associated with increased risk of all-cause mortality.

These findings emphasize the importance of an echocardiographic surveillance of ICD and PM recipients to anticipate the development of heart failure. In fact, although lead repositioning or extraction might be an option only at short-term after implantation, other therapeutic options, such as upgrade to biventricular pacemaker, optimization of heart failure medications or a surgical procedure of the tricuspid valve, might be considered in patients with significant TR and/or worsening of LV function.

Several limitations of the current study should be mentioned. First, the exact mechanism of lead-induced TR could not be confirmed in all patients. In addition, there remains unclear whether progression of RV remodeling would be the cause or the consequence of significant TR. Moreover, the time interval between echocardiographic evaluations of 1-1.5 years was chosen to ensure identification of both acute and long-term occurrence of significant TR, but may have still underestimated the incidence of this complication, particularly because patients who died within 1 year after implantation were excluded. The mode of death was not systematically available and the impact of significant lead-induced TR on cardiovascular mortality could not be assessed. Finally, prospective studies with larger patient populations and longer follow-up are needed.

In conclusion, a significant increased TR incidence was observed at follow-up after implantation of an RV lead in more than 35% of ICD and PM recipients. A significant lead-induced TR was associated with an impaired RV performance and with a higher incidence of long-term mortality and heart failure events. These findings suggest the importance of an echocardiographic follow-up in these patients in order to optimize patient management.

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