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Published in:
Circulation. Arrhythmia and electrophysiology

DOI:
10.1161/CIRCEP.118.007124

Published: 01/01/2019

Citation for pulished version (APA):
Beurskens, N. E. G., Tjong, F. V. Y., de Bruin-Bon, R. H. A., Dasselaar, K. J., Kuijt, W. J., Wilde, A. A. M., & Knops, R. E. (2019). Impact of Leadless Pacemaker Therapy on Cardiac and Atrioventricular Valve Function Through 12 Months of Follow-Up. *Circulation. Arrhythmia and electrophysiology*, *12*(5), e007124. https://doi.org/10.1161/CIRCEP.118.007124

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Impact of Leadless Pacemaker Therapy on Cardiac and Atrioventricular Valve Function Through 12 Months of Follow-Up

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BACKGROUND: Endocardial pacemaker leads and right ventricular (RV) pacing are well-known causes of tricuspid valve, mitral valve, and cardiac dysfunction. Lead-related adverse consequences can potentially be mitigated by leadless pacemaker (LP) therapy by eliminating the presence of a transvalvular lead. This study assessed the impact of LP placement on cardiac and valvular structure and function.

METHODS: Echocardiographic studies before and 12±1 months after LP implantation were performed between January 2013 and May 2018 at our center and compared with age- and sex-matched controls of dual-chamber transvenous pacemaker recipients.

RESULTS: A total of 53 patients receiving an LP were included, of whom 28 were implanted with a Nanostim and 25 with a Micra LP device. Tricuspid valve regurgitation was graded as being more severe in 23 (43%) patients at 12±1 months compared with baseline (P<0.001). Compared with an apical position, an RV septal position of the LP was associated with increased tricuspid valve incompetence (odds ratio, 5.20; P=0.03). An increase in mitral valve regurgitation was observed in 38% of patients (P=0.006). LP implantation resulted in a reduction of RV function, according to a lower tricuspid annular plane systolic excursion (P=0.003) and RV tricuspid lateral annular systolic velocity (P=0.02), and a higher RV Tei index (P=0.04). LP implantation was further associated with a reduction of left ventricular ejection fraction (P=0.03) and elevated left ventricular Tei index (P=0.003). The changes in tricuspid valve regurgitation in the LP group were similar to the changes in the dual-chamber transvenous pacemaker control group (43% versus 38%, respectively; P=0.39).

CONCLUSIONS: LP therapy is associated with an increase in tricuspid valve dysfunction through 12 months of follow-up; yet it was comparable to dual-chamber transvenous pacemaker systems. Furthermore, LP therapy seems to adversely impact mitral valve and biventricular function.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: echocardiography ■ leadless pacemaker therapy ■ mitral valve insufficiency ■ tricuspid valve insufficiency

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WHAT IS KNOWN?

- Transvenous right ventricular pacemaker therapy can worsen tricuspid and mitral regurgitation and alter ventricular function.
- Right ventricular leadless pacing therapy does not significantly impact tricuspid valve and ventricular function at 2 months of follow-up.

WHAT THE STUDY ADDS?

- Right ventricular leadless pacing therapy results in worsening tricuspid regurgitation and a reduction in ventricular function at 12 months of follow-up.
- The changes in leadless pacing-induced tricuspid regurgitation are similar to the changes in the transvenous dual-chamber pacemaker control group.
- The mechanical interference of the intracardiac leadless device on the tricuspid valve or its subvalvular apparatus is the primary cause because a more septal position was associated with aggravation of tricuspid regurgitation severity.

Lead-based conventional pacemaker therapy is associated with development or intensification of tricuspid valve (TV) regurgitation (TR) in 25% to 50% of cases.[1,2] The clinical presentation of TR varies widely, yet can result in incremental morbidity and mortality. Intensification of TR is likely a consequence of damage to the TV leaflets or subvalvular apparatus during lead implantation on one hand and the long-term mechanical impact of the transvalvular lead on the other hand.[3,4] Furthermore, studies implicate that right ventricular (RV) pacing–induced ventricular dyssynchrony is associated with an increase in TV incompetence, in addition to mitral valve (MV), and cardiac dysfunction in pacemaker recipients.[3,5–10]

Leadless pacemaker (LP) therapy was developed to address the limitations of standard lead-based pacing.[11,12] Lead-related TV dysfunction may be ameliorated by this novel approach because the continuous mechanical impact of the lead on the TV is potentially eliminated. Similar to conventional RV pacing systems, LPs are often placed in the RV apex because of its relative easy accessibility. LP therapy may, therefore, induce a similar abnormal electrical and mechanical activation pattern of the ventricles.

Studies evaluating mid- and long-term cardiac morphology and function after LP therapy are lacking. These studies are of paramount importance because they will provide interesting insights into the mechanisms of TR, MV regurgitation (MR), and ventricular dysfunction and to delineate whether these mechanisms are mechanically caused by the transvalvular leads or by electrical dyssynchrony from RV pacing.

Therefore, we sought to establish the effect of LP therapy (ie, Abbott, Nanostim and Medtronic, Micra) on heart structure and function at 12 months post-implant.

METHODS

Patients underwent an echocardiographic study before and 12±1 months after Nanostim or Micra LP implantation between January 2013 and May 2018 at the Amsterdam UMC, location Academic Medical Center. We used the data of a prospectively acquired population that comprised consecutive patients who underwent LP implantation at our center. A specific LP echocardiographic protocol was composed. The echocardiograms were performed in the setting of regular clinical care and were retrospectively assessed. Patients were excluded if echocardiographic image quality was insufficient for the evaluation of cardiac and valvular morphology. In addition, specific echocardiographic studies were excluded if its assessment was not feasible or unreliable (eg, Tei indices in patients with atrial fibrillation and deviating PR duration). In these patients, the remaining echocardiographic parameters were included in the analysis. As control group, we retrospectively collected data of patients who underwent conventional dual-chamber (DDD) pacemaker implant between January 2013 and 2018 at our center. DDD pacemaker patients who and had a preprocedural and follow-up echocardiographic assessment available were 1:1 age- and sex-matched using caliper matching (ie, 0.2). Implantation of the LP device was performed in the catheterization laboratory by 2 electrophysiologists, according to current recommendations.[13] Standard implantation techniques were used for the conventional pacemaker devices by different electrophysiologists in the catheterization laboratory at our center.

The study conforms to the ethical guidelines of the Declaration of Helsinki. Ethical approval was obtained by the Medical Ethics Committee at the Academic Medical Center–University of Amsterdam, the Netherlands. All patients provided written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Echocardiographic Protocol and Assessment

At our center, a Vivid 7 or 9 machine (GE Vingmed Ultrasound AS, Horten, Norway) was used for echocardiographic image acquisition. Echocardiographic recordings were performed using a 1.6- to 3.2-MHz transducer (System 7 or 9; GE Healthcare, Milwaukee, WI). These recordings were digitized and subsequently assessed by an experienced echocardiographer. All echocardiographic images and indices were obtained according to current guidelines.[14] The mean value of 3 repetitive measurements was used for patients in sinus rhythm and 5 measurements in those with atrial fibrillation.

In patients with no atrial fibrillation, for determining the degree of MR, quantitative data from color Doppler involving the color flow jet area in the left atrium and pulmonary vein flow were used. The TR was assessed according to Lancelotti European Association of Cardiovascular Imaging Echo Guidelines. The degree of TR was based on the color flow jet area in the right atrium by using the apical 4-chamber

view in addition to continuous-wave Doppler, pulsed-wave Doppler, peak tricuspid systolic inflow, vena contracta diameter, and liver vein flow. TR and MR severity were categorized into 5 groups (ie, 0–4; 0=none, 1=mild, 2=mild to moderate, 3=moderate to severe, and 4=severe). Continuous-wave Doppler of the TR jet was used for the estimation of the systolic pulmonary artery pressure using the modified Bernoulli equation and right atrial pressure, which was estimated in consonance with inferior vena cava size.

The left ventricular (LV) ejection fraction (LVEF) was determined according to the Simpson rule. RV function was evaluated by using several parameters, including tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity (S′), and by the RV Tei index (ie, myocardial performance index). The M-mode apical 4-chamber imaging mode was used for the assessment of the TAPSE, wherein the cursor was oriented to the junction of the RV free wall and TV plane. TAPSE was determined by tricuspid annulus displacement from end-diastole to end-systole.[15,16] Pulsed-wave tissue Doppler using the apical 4-chamber imaging mode was used for the measurement of RV S′.[17] The RV Tei was calculated by the difference in the interval between cessation and onset of tricuspid flow velocity and the RV outflow velocity time. This difference is then divided by the RV outflow velocity time.[18]

Statistical Analysis

Data are presented as numbers and percentages for categorical variables. For continuous variables, mean±SD and median (interquartile range) are shown. Echocardiographic parameters before LP and DDD pacemaker implantation were compared with the follow-up echocardiographic indices using the Wilcoxon signed-rank test. Continuous variables of subgroups were compared using Mann-Whitney *U* test or independent samples *t* test, dependent on their distribution. Categorical variables of subgroups were compared using Fisher exact test or χ^2 test. The logistic regression test was used to predict the relationship of potential predictors, such as type of device, percentage pacing, pacing during echocardiogram, and cardiac dimensions, associated with increased TR.

For the assessment of the intraobserver variability of the primary outcome (ie, TR), one observer (R.H.A. de Bruin-Bon) reevaluated 25 randomly selected echocardiographic studies. The observer was fully blinded, and the interval between initial and reassessment was >2 months. For the interobserver variability, 25 randomly selected echocardiograms were evaluated by fully blinded experienced echocardiographers. The observer variability was assessed by using the 2-way mixed intraclass correlation coefficient.

Statistical significance was considered achieved at a P <0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows (or Macintosh), version 24.0; Armonk, NY, IBM Corp.

RESULTS

Study Cohort

An overview of the baseline characteristics is displayed in Table 1. Preimplant and postimplant echocardiographic studies were done in 56 patients who underwent LP implantation between January 2013 and May 2017. In 3 patients, the echocardiographic quality was insufficient for the assessment of cardiac and valvular morphology, leaving a final cohort of 53 LP recipients (age, 80.5±7.92 years; 37 [70%] men; body mass index, 25.4±3.66 kg/m^2).

Table 1. Baseline Characteristics

	LP (n=53)	DDD-PM (n=53)	*P* Value
Age, y	80.5±7.92	79.3±6.89	0.59
Men, n (%)	37 (70%)	37 (70%)	1.0
BMI, kg/m^2	25.4±3.66	25.6±4.39	0.73
Pacing indication, n (%)			<0.001
Bradycardia associated with persistent or permanent atrial tachyarrhythmia	28 (53%)	0 (0%)	
Sinus node dysfunction	17 (32%)	19 (36%)	
Atrioventricular block	8 (15%)	29 (55%)	
Other	0 (0%)	5 (9%)	
Cardiovascular disease history, n (%)			
Congestive heart failure	5 (9%)	3 (6%)	0.46
Coronary artery disease	3 (6%)	2 (4%)	0.65
Hypertension	17 (32%)	29 (54%)	0.05
Myocardial infarction	2 (4%)	4 (8%)	0.40
Cardiomyopathy	2 (4%)	1 (2%)	0.56
Other comorbidities, n (%)			
COPD	2 (4%)	2 (4%)	1.00
Diabetes mellitus	6 (11%)	13 (25%)	0.08
Renal dysfunction	4 (8%)	3 (6%)	0.69
CVA	2 (4%)	3 (6%)	0.65
LP			
Nanostim, n (%)	28 (53%)	NA	
Micra, n (%)	25 (47%)	NA	

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebellar vascular accident; DDD-PM, dual-chamber pacemaker; LP, leadless pacemaker; and NA, not applicable.

The age- and sex-matched control group included 53 patients who underwent conventional DDD pacemaker implant at our center. The lead-based DDD pacemaker control group included 37 (70%) men, had a mean age of 79.3±6.89 years, and a body mass index of 25.6±4.39 kg/m^2. The mean age, sex, and body mass index were similar for the patients who underwent LP and transvenous DDD pacemaker implantation (Table 1). As expected, there was a significant difference in pacing indication between groups (P<0.001). In the DDD pacemaker group, hypertension was more prevalent compared with the LP group (P=0.05).

LP Implantation

A total of 28 Nanostim and 25 Micra devices were implanted with adequate electrical parameters. In 42

Table 2. Echocardiographic Indices Before and at 12 mo After Leadless Pacemaker Implantation (Total Cohort)

Echocardiographic Indices	Before Implantation	12 mo After Implantation	*P* Value
LV end-diastolic diameter, mm; mean±SD	48.6±7.72	48.4±7.31	0.75
LV end-systolic diameter, mm; mean±SD	31.4±7.51	31.8±7.2	0.33
LV end-diastolic septum thickness, mm; mean±SD	11.4±2.17	10.5±1.66	0.74
LV end-diastolic volume, mL; mean±SD	92.4±32.9	85.8±25.7	0.68
LV end-systolic volume, mL; mean±SD	43.2±18.1	43.7±16.4	0.29
LVEF, %; mean±SD	53.5±8.55	50.2±8.55	0.03
LV Tei, mean±SD (n=33)	0.48±0.12	0.69±0.27	0.003
LVOT VTI, cm; mean±SD (n=47)	21.4±3.70	20.2±5.20	0.37
LA volume, mL/m^2, mean±SD	50.6±23.9	48.8±21.6	0.84
RV end-diastolic diameter, mm; mean±SD	42.7±6.26	43.6±5.56	0.10
TAPSE, mm; mean±SD	18.6±6.81	16.24±6.52	0.003
S wave,* cm/s; mean±SD (n=35)	11.8±3.04	10.9±2.49	0.02
RV Tei, mean±SD (n=36)	0.40±0.10	0.50±0.16	0.04
SPAP, mm Hg; mean±SD	32.3±8.72	32.0±8.91	0.21
RA area, cm^2; mean±SD	21.6±6.72	22.4±6.79	0.14
MV disease (n=44)			0.006
No	9 (20%)	4 (9%)	
Mild regurgitation	22 (50%)	21 (47%)	
Mild-to-moderate regurgitation	11 (25%)	14 (32%)	
Moderate-to-severe regurgitation	2 (5%)	3 (7%)	
Severe regurgitation	0 (0%)	2 (5%)	
Aortic valve disease (n=48)			0.07
No	25 (52%)	22 (46%)	
Mild regurgitation	20 (42%)	19 (40%)	
Moderate regurgitation	3 (6%)	7 (14%)	
Severe regurgitation	0 (0%)	0 (0%)	
TV disease			<0.001
No	6 (11%)	1 (2%)	
Mild regurgitation	26 (49%)	18 (34%)	
Mild-to-moderate regurgitation	14 (26%)	20 (38%)	
Moderate-to-severe regurgitation	7 (13%)	14 (26%)	
Severe regurgitation	0 (0%)	0 (0%)	

LA indicates left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve; RA, right atrium; RV, right ventricle; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve; and VTI, velocity time integral.

*S wave, derived tricuspid lateral annular systolic velocity.

patients, the LP was adequately placed in the RV within 1 deployment. The mean LP procedure duration was 39.4±12.8 minutes. The LP procedure duration was defined as the time from access until removal of the introducer. The device was placed in 42 (79%) patients in the RV apex, in 8 (15%) patients in the apical septum, and in 3 (6%) patients in the septum of the RV. There was 1 LP recipient who had a complication after the Nanostim procedure. The patient experienced an arteriovenous fistula at the access site but this did not result in longer hospitalization.

TV Regurgitation

TR severity was graded as being more severe in 23 (43%), unchanged in 27 (51%), and less severe in 3 (6%) patients (P<0.001) at 12 months after LP implant (Figures 1 and 2). More severe TR was observed in 12 (43%) of the Nanostim (P=0.007) and 11 (44%) of Micra recipients (P=0.005) at 12 months compared with baseline. Logistic regression revealed that a more right ventricular septal position compared with an apical position of the LP (odds ratio [OR], 5.20; 95% CI, 1.22–22.2; P=0.03) was associated with worsening TR. In addition, a further distance from the proximal end of the device to the TV based on echocardiography seems to positively impact TV function (OR, 0.96; 95% CI, 0.92–1.01; P=0.09). The need for multiple device deployments did not interfere with TV function at last follow-up (OR, 1.59; 95% CI, 0.40–6.26; P=0.51). In addition, longer procedural time was not associated with new-onset or worsening TV dysfunction (P=0.73). There was no significant correlation between the percentage of paced beats and TV competence (OR, 1.00; 95% CI, 0.98–1.01; P=0.94) and between patients who were paced during follow-up echocardiogram (n=21) and increasing TR (OR, 0.63; 95% CI, 0.15–2.66; P=0.63). Of 14 patients who had a pacing percentage of <10%, 7 (50%) patients had an increase in TV incompetence. The changes in TR and MR for different ranges of ventricular pacing have been added to Table I in the Data Supplement. RV (OR, 1.01; 95% CI, 0.91–1.1; P=0.84) and right atrial dimensions (OR, 1.01; 95% CI, 0.93–1.09) did not result in an increase of TR regurgitation. An increase in systolic pulmonary artery pressure did not correlate with worsening TR (OR, 1.40; 95% CI, 0.37–5.26; P=0.62). Lastly, aggravation of MR was not related to an intensification of TR (OR, 0.50; 95% CI, 0.15–1.75; P=0.28). The preimplant and postimplant echocardiographic assessments of the total cohort are listed in Table 2 and separately for the Nanostim and Micra in Table 3.

In the control group, TR severity was graded as being more severe in 20 (38%), unchanged in 29 (55%), and less severe in 4 (7%) patients (P=0.02) at 16±7.6 months after implant. There were no statistically differences between LP and conventional pacemaker recipients with respect to age, sex, and body mass index. LP recipients were equally prone to increasing TV dys-

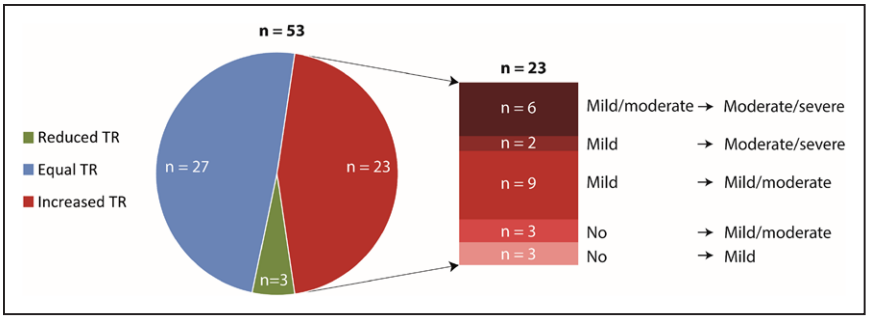

Figure 1. The development of tricuspid valve regurgitation (TR) in leadless pacemaker (LP) recipients: out of the total cohort, 23 patients had an intensification of TR at 12 mo after Nanostim or Micra LP implantation.
In 5 patients, TR severity was scored 2 gradations higher at follow-up compared with baseline, and in the remaining patients, the degree of TR was graded 1 category higher.

function compared with conventional DDD pacemakers (43% versus 38%; *P*=0.395). The follow-up duration was significantly longer for the control group (ie, 16 months) versus the LP group (ie, 12 months; *P*<0.001). An overview of the development of TR in the LP and control groups is illustrated in Table 4.

MV Regurgitation

The degree of MR was assessed as being more severe in 17 (38%), unchanged in 24 (55%), and less severe in 3 (7%) cases (*P*=0.006) at 12 months compared with the pre-LP implant echocardiogram. The prevalence of new-onset or worsening MR was high in patients with a pacemaker rhythm on electrocardiography at the follow-up visit, namely in 57% of cases. The mean percentage of pacing in the group of patients with aggravating MR was higher compared with those with an equal degree of MR (ie, 48±10% versus 43±7.5%, respectively). There were no significant changes observed in LV end-diastolic volume (92.4±32.9 versus 85.8±25.7 mL; *P*=0.68) and left atrial volumes (50.6±23.9 versus 48.8±21.6 mL; *P*=0.84) between the follow-up visit and baseline. The changes in MR and TR for different ranges of ventricular pacing have been included to Table I in the Data Supplement.

Left and RV Function

The Wilcoxon signed-rank test revealed that TAPSE (*P*=0.003) and RV S′ (*P*=0.02) significantly decreased after LP therapy. The RV Tei index increased significantly after LP implant (*P*=0.04). An LVEF reduction (*P*=0.03) and an increase in LV Tei (*P*=0.003) were observed at 12 months compared with pre-LP placement. In 11 (34%) patients, the LVEF decreased >10%. The percentages of pacing in these patients were as follows: 5 had 100% pacing, 1 had 89% pacing, 1 had 60% pacing, and 4 patients had a pacing percentage of <20%.

Observer Variability

For the intraobserver variability measurements, the correlation for TR was 0.84 (95% CI, 0.64–0.93; *P*<0.001). For the interobserver assessments, the correlation for TR was 0.86 (95% CI, 0.67–0.94; *P*<0.001), for MR was 0.93 (95% CI, 0.85–0.97; *P*<0.001), for LV end-diastolic diameter was 0.96 (95% CI, 0.91–0.98; *P*<0.001), for RV end-diastolic diameter was 0.90 (95% CI, 0.70–0.96; *P*<0.001), for right atrial area was 0.94 (95% CI, 0.85–0.98; *P*<0.001), and for TAPSE was 0.94 (95% CI, 0.83–0.98; *P*<0.001). The observer variability measurements have been added to Table II in the Data Supplement.

DISCUSSION

The current study elicited several major findings. To our knowledge, this is the first and the largest study to document intensification of TR after Nanostim and Micra LP therapy. Our data suggest that the mechanical impact of the device near the TV apparatus is the most likely cause of this phenomenon because –the recommended- more septal position compared with apical position of the LP was associated with an increase in TV incompetence. In addition, other factors such as procedural characteristics, pacing percentage, paced rhythm during echocardiogram, and changes in systolic pulmonary artery pressure, MR, and cardiac morphology played no significant role in the worsening of TR. We further observed that LP implantation was associated with an aggravation of MR, RV, and LV dysfunction through 12 months of follow-up, which may be a result of RV pacing–induced ventricular dyssynchrony.

TV Regurgitation

Conventional defibrillator and pacemaker leads need to be placed across the TV, which can result in a degree of iatrogenic TR. TR is independently related to an increasing prevalence of mortality and heart failure hospitalization, even after accounting for well-known causes of TR such as left-sided heart failure and RV dilation.[4,19] Studies show that in patients with cardiac implantable electronic devices, the prevalence of new-onset or worsening TR increases with 20% to 50% compared with patients without a pacemaker.[1,2] In line with previous studies, we showed that lead-based DDD pacemaker therapy was associated with worsening TV function. TV dysfunction after conventional pacemaker

Table 3. Echocardiographic Indices Before and at 12 mo After Leadless Pacemaker Implantation (Nanostim and Micra Separately)

Echocardiographic Indices	Nanostim			Micra		
	Baseline	12 mo	*P* Value	Baseline	12 mo	*P* Value
LV end-diastolic diameter, mm; mean±SD	49.9±7.32	50.2±6.73	0.55	47.1±8.30	46.8±7.51	0.79
LV end-systolic diameter, mm; mean±SD	32.6±6.83	33.4±6.72	0.48	30.2±8.09	30.2±7.29	0.46
LV end-diastolic septum thickness, mm; mean±SD	11.2±2.20	11.3±1.61	0.88	11.7±2.05	12.0±2.49	0.77
LV end-diastolic volume, mL; mean±SD	93.2±32.2	90.5±24.4	0.95	91.2±35.1	82±28.7	0.19
LV end-systolic volume, mL; mean±SD	43.3±17.8	45.4±14.8	0.14	43.1±19.2	43.1±19.8	1.00
LVEF, %; mean±SD	54.1±8.56	50.3±7.48	0.01	52.6±9.77	50.2±9.93	0.68
LV Tei, mean±SD	0.48±0.13	0.66±0.26	0.05	0.48±0.11	0.74±0.29	0.03
LVOT VTI, cm; mean±SD	20.2±3.83	20.1±4.25	0.71	22.8±3.11	20.9±6.53	0.32
LA volume, mL/m^2; mean±SD	54.8±24.8	50.9±18.1	0.88	44.91±22.2	48.3±27.3	0.97
RV end-diastolic diameter, mm; mean±SD	42.1±6.65	43.2±5.19	0.14	43.7±5.67	44.1±6.23	0.48
TAPSE, mm; mean±SD	19.9±4.54	18.2±4.33	0.01	16.8±8.64	14.1±7.81	0.08
S wave,* cm/s; mean±SD	11.4±3.23	11.2±2.07	0.31	12.4±2.81	10.6±3.11	0.01
RV Tei, mean±SD	0.42±0.10	0.48±0.14	0.44	0.36±0.08	0.52±0.19	0.04
SPAP, mm Hg; mean±SD	31.7±10.1	31.6±5.96	0.83	33.1±6.70	32.5±11.6	0.05
RA area, cm^2; mean±SD	22.3±6.34	23.2±5.91	0.23	20.7±7.19	21.4±7.75	0.39
MV disease			0.005			0.37
No	4	2		5	2	
Mild regurgitation	12	8		10	13	
Mild-to-moderate regurgitation	4	7		7	7	
Moderate-to-severe regurgitation	1	2		1	1	
Severe regurgitation	0	2		0	0	
Aortic valve disease			1.00			0.02
No	13	13		12	9	
Mild regurgitation	12	12		8	7	
Moderate regurgitation	1	1		2	6	
Severe regurgitation	0	0		0	0	
TV disease			0.007			0.005
No	4	0		2	1	
Mild regurgitation	11	9		15	9	
Mild-to-moderate regurgitation	7	11		7	9	
Moderate-to-severe regurgitation	6	8		1	6	
Severe regurgitation	0	0		0	0	

LA indicates left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve; RA, right atrium; RV, right ventricle; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve; and VTI, velocity time integral.

*S wave, derived tricuspid lateral annular systolic velocity.

therapy is likely a consequence of mechanical interaction of the transvalvular lead with the TV apparatus, TV damage during implantation, or cardiac remodeling from heart failure. LP therapy is a promising approach of cardiac pacing, consisting of a miniaturized device completely placed inside the RV. It has been suggested that the absence of a transvalvular lead potentially reduces inadequate leaflet coaptation and mechanical impact on the TV apparatus. The immediate impact of leadless pacing on cardiac function and TR based on echocardiography has been studied by Salaun et al.[20] They concluded that there were no significant changes in cardiac morphology and function, including TR and MR at 2 months after LP implantation. There are differences between Salaun et al and this study that should be emphasized. Their study cohort involved 23 patients, whereas we included 53 patients. Moreover, their echocardiographic assessments were performed 2 months after the LP procedure, whereas our echocardiographic studies were obtained at 12 months of follow-up. In contrast, this study demonstrated that LP therapy is associated with an aggravation of TR severity. In this study, LP recipients were equally prone to worsening TV function compared with the

Table 4. Development of TV Regurgitation After LP and Conventional DDD Pacemaker Therapy

	LPs (n=53)			Conventional DDD Pacemakers (n=53)			*P* Value
TV Disease	**Baseline**	**FU**	***P* Value**	**Baseline**	**FU**	***P* Value**	**0.395**
No	6 (11%)	1 (2%)	<0.001	10 (19%)	2 (4%)	0.02	
Mild regurgitation	26 (49%)	18 (34%)		27 (51%)	31 (59%)		
Mild-to-moderate regurgitation	14 (26%)	20 (38%)		12 (23%)	16 (30%)		
Moderate-to-severe regurgitation	7 (13%)	14 (26%)		4 (8%)	1 (2%)		
Severe regurgitation	0 (0%)	0 (0%)		0 (0%)	3 (6%)		

DDD-PM indicates dual-chamber pacemaker; LP, leadless pacemaker; and TV, tricuspid valve.

lead-based pacemaker control group. Yet, caution is advised regarding the interpretation of this observation because the follow-up duration of the LP group was significantly shorter compared with the conventional pacemaker group. Four potential mechanisms are involved in TV dysfunction after LP implantation: (1) TV damage during implantation, (2) ongoing mechanical impact of the device on the TV or its subvalvular apparatus, (3) pacing-induced RV dyssynchrony, illustrated in Movie I in the Data Supplement, or (4) other factors.

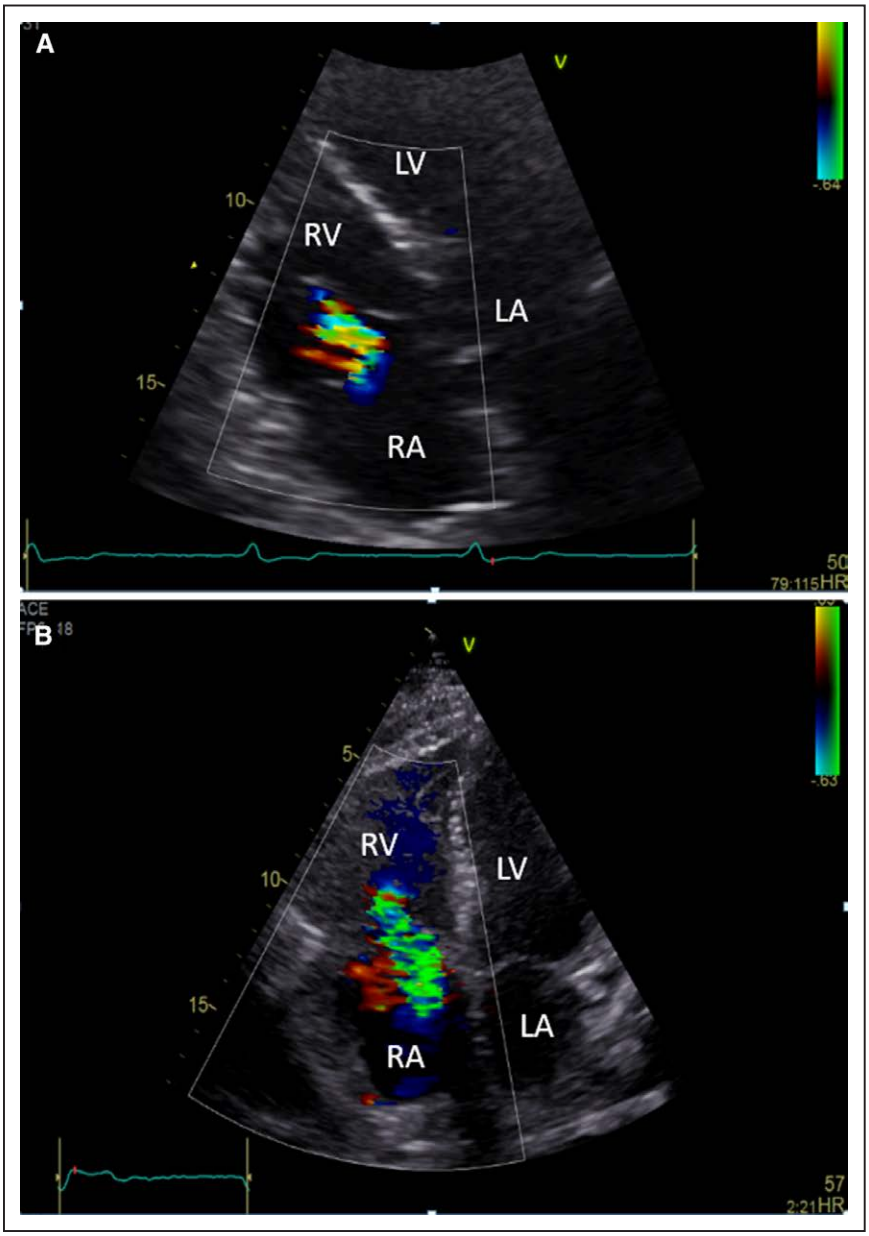

Figure 2. Echocardiographic evaluation of tricuspid valve regurgitation (TR) severity after leadless pacemaker (LP) therapy: deterioration of tricuspid valve function in a patient after LP therapy.
TR severity was evaluated by transthoracic echocardiography at baseline (**A**) and 12 mo post-LP implant (**B**). The baseline echocardiogram illustrates mild TR, whereas moderate/severe TR can be seen in the follow-up echo in this LP recipient. LA indicates left atrium; LV, left ventricle; RA, right atrium; and RV, right ventricle.

(1) There are several TV complications that may occur during the LP implant procedure including leaflet perforation, chordal tearing, and papillary muscle injury.[4] One can argue that multiple device deployments and longer manipulation of the device before reaching adequate electrical parameters may increase the risk for surgical injury to the TV apparatus, but neither procedure duration nor multiple device manipulations at implant were associated with an increase in TV incompetence. Moreover, Salaun et al[20] observed no significant TV dysfunction in 23 patients studied 2 months after LP implant. Their data, combined with our observations, suggest that LP-related TV dysfunction is not typically an acute complication of the implant procedure; it may take some time to develop. (2) Our data suggest that mechanical interference of the LP device with the TV subvalvular apparatus may be the primary cause of worsening TR over time. Patients with a more septal compared with apical position of the LP were 5× more prone to worsening TR. The impact of the intracardiac device near the TV may prevent adequate leaflet mobility or impingement. The pathogenesis of this mechanical LP-related TV dysfunction may be explained by entanglement of the leadless device with the chordae tendineae or the direct interaction of the intracardiac device on the leaflets. In addition, encapsulation of the LP may result in loss of leaflet mobility or coaptation because of adhesive interactions between fibrotic tissue formation around the device and subvalvular endocardial structures. (3) The role of RV pacing itself using conventional transvenous leads in causing TR has been controversial.[21] The majority of conventional pacemaker studies demonstrated that the number of paced beats does not relate with worsening TR,[22–24] whereas others have suggested that pacing-induced dyssynchrony may result in secondary TR.[25,26] The pathogenesis of this secondary TR may be explained by that pacing-induced dyssynchrony potentially results in LV diastolic and systolic dysfunction or MR, which, subsequently, raises left-sided filling pressure and pulmonary artery pressure, resulting in the secondary TR.[4] In line with previous studies evaluating TV dysfunction after lead-based pacemaker therapy, we demonstrated that the percentage of RV pacing did not correlate with new-onset or worsening TR. This was confirmed by the fact that in the group of patients with the lowest pacing percentages, therefore, excluding pacing-induced TR, the prevalence of TR aggravation was common. Furthermore, patients who were paced during the follow-up echocardiogram were not more prone to the development of TR in the current cohort. (4) There are several potential secondary causes of TV insufficiency, such as the development of pulmonary artery hypertension, RV dilatation, left-sided heart valve disease or heart failure, and chronic lung disease.[4] TR development did not seem to result from any of these factors in the current study. There were no patients who had organic TV disease that can account for TR such as rheumatic TV disease or TV endocarditis. The presence of other cardiac diseases did not interfere with the degree of worsening TV function in the current cohort. In addition, there were no other cardiac interventions during the FU period that can lead to worsening TR. This suggests that the LP by itself results in primary new-onset or worsening TR.

MV Regurgitation

In addition to TR aggravation, we observed an increase in prevalence of MR after LP placement. The majority of patients with new-onset or worsening MR had a paced rhythm on electrocardiography at the follow-up visit, which might be an explanation for this observation. Although the pacing percentage was higher in the worsening-MR group compared with the equal-MR group, it reached no statistical significance. Therefore, it does not permit us to draw definite conclusions on the primary cause of the increase in MV incompetence. However, it has been shown in conventional pacemaker cohorts that dyssynchronous LV electromechanical activation induced by RV pacing results in LV remodeling that can cause LV dilatation and a reduction in the LVEF. The former results in mitral annular dilatation and anomalous leaflet coaptation, which is responsible for causing MR.[24,27–29] MR in return causes further reduction in LVEF and increased LV dimensions.[24]

LV and RV Function

Multiple studies have evaluated the impact of lead-based RV pacing on cardiac function.[30–33] Several studies suggested that pacing-induced mechanical dyssynchrony is associated with occurrence or worsening of left-sided heart failure and hospitalization, especially in patients with heart failure.[34] In contrast, Alizadeh et al[21] documented that the LV function remained in normal limits in pacemaker patients with a preserved ejection fraction at baseline through 4 years of follow-up. We found a significant LVEF reduction of 3.2% after LP therapy. One may argue what the clinical relevance of this observation is. Yet, we showed that in 1 patient, new-onset reduced LVEF (ie, <40%) developed after LP implantation with a follow-up of 12 months. Furthermore, a substantial reduction in LVEF (ie, >10% reduction) was not uncommon in our study population, yet no patients developed symptoms of LV dysfunction. Our data further showed that there was a significant reduction in RV function after LP implantation. There are several mechanisms that are involved in potential harmful effects of RV pacing on cardiac function. In general, both the electrical and

mechanical activation patterns of the ventricles are changed during RV pacing, which result in less effective ventricular contraction and subsequently in a reduction of cardiac output.[3,10] Furthermore, dyssynchronous RV and LV electromechanical activation may induce changes in coronary blood flow, hemodynamics, remodeling, perfusion, and metabolism, which may lead to worsening heart function.[3,10] To date, it remains unknown why some patients acutely develop pathological dyssynchrony after RV pacing, and why others are spared.[10]

Limitations

The current study has some limitations. First, in this single-center study, LP implantations were performed by 2 operators. Data on heart structure and function after LP therapy from different institutions and operators are required to determine the validity of the present results. Second, the immediate impact of LP placement on TV function was not assessed because no echocardiogram was performed before discharge. Therefore, iatrogenic damage to the TV could have been missed. However, procedural characteristics such as longer manipulation of the device and number of device deployments were not associated with intensification of TR. Third, echocardiographic evaluation of RV and TV morphology and function remains challenging. Yet, echocardiography is the first choice of diagnostic tools in the follow-up of these patients. Fourth, the changes in TR and MR for different ranges of ventricular transvenous pacing are currently not available. Lastly, a direct prospective comparison of cardiac and atrioventricular valve function between lead-based single-chamber pacemakers and LPs at the same follow-up time was not performed. Therefore, it does not permit us to draw definite conclusions whether LP has a more negative, equally, or more positive impact on heart structure and function compared with conventional pacemaker systems. This should be investigated in future studies.

Conclusions

LP therapy is associated with an aggravation of TR severity at 12 months of follow-up, despite the circumvention of transvalvular leads. Our data suggest that the mechanical interference of the device on the TV or its subvalvular apparatus is the primary cause, as a more septal position was correlated with an increase in TV incompetence. The changes in TR in the LP group were similar to the changes in the transvenous DDD pacemaker control group. We further observed a decrease in MV and biventricular function, which may be a consequence of abnormal electrical and mechanical activation patterns of the ventricles induced by LP therapy. These results are highly relevant as they contradict expected performance of LP therapy and warrant further investigation.

ARTICLE INFORMATION

Received September 19, 2018; accepted March 5, 2019.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.118.007124.

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Disclosures

Dr Tjong reports consulting fees from Boston Scientific Corporation, Inc, and Abbott. Dr Knops reports consulting fees, research grants, and honoraria for Boston Scientific and consulting fees and research grants with Medtronic and St. Jude Medical. The other authors report no conflicts.

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