Nonapical Right Ventricular Pacing Is Associated with Less Tricuspid Valve Interference and Long-Term Progress of Tricuspid Regurgitation

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Background: Tricuspid regurgitation (TR) is a well-known complication after permanent pacemaker implantation. The aim of this study was to compare the degree of TR and the relationship of lead position across the tricuspid valve (TV) between patients with right ventricular apical (RVA) and non-RVA pacing determined by three-dimensional echocardiography.

Methods: Conventional and three-dimensional echocardiography was performed in 284 patients to determine the change in TR severity following permanent pacemaker implantation. Transvenous lead locations were based on fluoroscopic images. This was a retrospective study, and the selected pacing mode was not randomized.

Results: RVA pacing had more frequent severe TR (37.9% vs 25.7%, $P = .03$) compared with non-RVA pacing. Severe TR occurred in 9.7%, 12.6%, and 58.8% of patients when the lead passed through the middle, between the commissures, and impinging the TV leaflets, respectively. Non-RVA leads were more likely to be positioned in the middle of the TV (30.3% vs 12.1%, $P < .01$) and had the lowest chance of leaflet impingement (33.6% vs 51.5%, $P < .01$) compared with RVA leads. RVA pacing was associated with worsening of grade $\geq$2 TR severity compared with non-RVA pacing (42.4% vs 27.6%, $P < .01$). A TV lead passage angle of -15° to 15° minimized TR.

Conclusions: Pacing-induced TR is more prevalent with RVA than non-RVA pacing. Preferential lead impingement on the TV leaflet, as determined by TV lead passage angle, can explain the development and progression of pacing-induced TR. (J Am Soc Echocardiogr 2020;33:1375-83.)

Keywords: Permanent pacemaker, Tricuspid regurgitation, Right ventricular apical pacing, Three-dimensional echocardiography

Tricuspid regurgitation (TR) is a known complication of permanent pacemaker (PPM) and implantable cardioverter-defibrillator devices, with a prevalence of up to 39%.[1,2] The prevalence of devices related to TR will likely increase further because of prolonged life expectancy and subsequently increased implantation number.[3] Interference of the tricuspid valve (TV) by transvenous endocardial leads has been proposed to be one of the major mechanisms of TR after device implantation.[4] Results of three-dimensional echocardiography (3DE), which enables detailed en face visualization of the TV, have revealed that the lead route and position at the TV determine the occurrence of lead-induced TR.[1,5,6]

Currently, transvenous endocardial leads are usually placed at the right ventricular (RV) apex, although alternative sites (including the RV septum and the RV outflow tract) have been proposed to be more physiological for a variety of reasons, including better electrical activation sequence, narrower paced QRS duration, fewer perfusion defects, and better preservation of left ventricular function.[7-10] Nonetheless, the degree of lead-induced TR and the benefit of lead position at the TV in RV apical (RVA) versus non-RVA pacing has received less attention. It is uncertain whether lead placement in

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Abbreviations

3DE = Three-dimensional echocardiography

AF = Atrial fibrillation

CW = Continuous-wave

PPM = Permanent pacemaker

RA = Right atrial

RV = Right ventricular

RVA = Right ventricular apical

TR = Tricuspid regurgitation

TV = Tricuspid valve

VC = Vena contracta

Vp% = Ventricular pacing percentage

the right ventricle can affect lead passage across the TV and influence the development of TR. The aim of the present study was to compare the prevalence and worsening of TR and the lead-leaflet relationship using 3DE in patients with RVA and non-RVA pacing.

METHODS

Study Population

A total of 395 patients who underwent pacemaker implantation at Queen Mary Hospital in Hong Kong were retrospectively identified, and all underwent preimplantation conventional transthoracic echocardiography. Patients with implantable cardioverter-defibrillators and biventricular pacemakers were not included in the present study. Patients were excluded if they had preimplantation severe TR (n = 10), adverse lead events including lead replacement (n = 14), lead repositioning (n = 3), or additional RV leads (n = 39), or single-chamber atrial pacemakers (n = 4). A total of 325 patients subsequently underwent postimplantation conventional echocardiography and 3DE from April 2014 to December 2018. Those with inadequate echocardiographic image quality (n = 41) for analysis were further excluded. As a result, 284 patients were eligible for final analysis. The study was part of the Chinese Valvular Heart Disease Study to evaluate the pattern of disease, pathophysiology, and clinical outcomes of valvular heart diseases.[11] This study was approved by the ethics committee of the West Cluster Hospital Authority of Hong Kong.

Clinical Parameters

Implantation procedure and baseline clinical data on preimplantation variables were retrieved from the electronic medical records. The selected pacing mode was based on individual cardiologist decision and was not randomized. Conventional cardiovascular risk factors such as a history of diabetes mellitus, hyperlipidemia, hypertension, and smoking status were documented. The occurrence of atrial fibrillation (AF) before and after implantation was also retrieved for each subject from his or her clinical record. At our center, all non-RVA leads were positioned toward the RV septum, guided by a posterior-pointing lead tip in the left anterior oblique view, as previously described.[10] The final lead position was ascertained by chest radiography in the posteroanterior view according to the published recommendation (Figure 1).[12,13] Briefly, the region from the pulmonary artery bulge to the inferior border of the cardiac silhouette was divided into three parts by horizontal lines. The superior third was the RV outflow tract, the middle third was the midseptum, and the inferior third was the RV apex. RVA pacing was defined when the electrode was positioned in the RV apex (n = 132); non-RVA pacing was considered when the electrode was positioned in the midseptum (n = 141) or RV outflow tract (n = 11). From the same chest radiographic study, the lead passage angle across the TV was measured as a surrogate for the direction of passage through the TV to the right ventricle (Figure 1). An imaginary horizontal line is drawn at the level of the TV, where the passage angle is positive if the lead is directed cranially toward the RV outflow tract and negative if the lead is directed caudally toward the RV apex. Ventricular pacing percentage (Vp%) was defined according to the last pacemaker interrogation that was performed every 6 months following implantation. Patients were considered highly pacing dependent if Vp% exceeded 90%.[14]

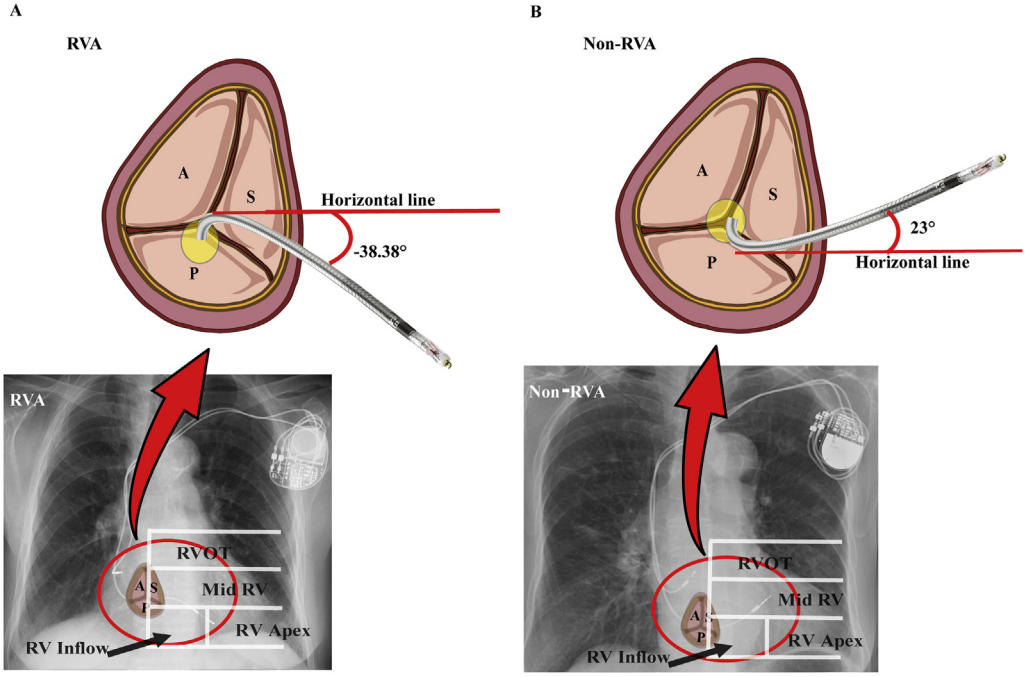


Figure 1 Chest radiography of (**A**) RVA pacing lead passage across the TV and (**B**) non-RVA pacing lead passage across the TV. *A*, Anterior; *Mid*, middle; *P*, posterior; *RVOT*, RV outflow tract.

HIGHLIGHTS

- Non-RVA and RVA pacing was more likely to be in the M and P positions, respectively.
- Lead in the P position was associated with severe TR compared with the M position.
- RVA pacing with Vp > 90% was associated with severe TR and increased worsening of TR.
- Lead passage angle -15° and 15° was associated with M passage

Transthoracic Two-Dimensional Echocardiography

Conventional echocardiography was performed on all patients using a commercially available echocardiographic system (Vivid E9; GE Vingmed Ultrasound, Horten, Norway). All images were analyzed offline using EchoPAC version 112.0 (GE Vingmed Ultrasound). Left ventricular volume, left ventricular ejection fraction, right atrial (RA) area, RV end-diastolic area, RV end-systolic area, RV fractional area change, and tricuspid annular diameter were measured according to current recommendations.[15] Pulmonary artery systolic pressure was estimated from peak TR velocity on continuous-wave (CW) Doppler using the modified Bernoulli equation: pulmonary artery systolic pressure = $4V^2$ + RA pressure.[16] Color/pulsed-wave and CW Doppler was used and TR was evaluated in apical four-chamber views and RV inflow and parasternal short-axis views at the aortic valve level. Hepatic venous flow was sampled using pulsed-wave Doppler. Grading of TR was ascertained using a multiparametric approach including qualitative, semiquantitative, and quantitative parameters measured on two-dimensional, color, CW, and pulsed-wave Doppler data based on the 2017 update of the American Society of Echocardiography recommendations for the noninvasive evaluation of native valvular regurgitation.[17] Vena contracta (VC), jet area, effective regurgitant orifice area, TR volume, and proximal isovelocity surface area radius were measured according to recommendations. The following were considered consistent with mild TR: (1) VC < 0.3 cm, (2) proximal isovelocity surface area radius < 0.4 cm at a Nyquist limit of 30 to 40 cm/sec, (3) incomplete TR jet by CW Doppler, (4) systolic flow dominance in the hepatic veins, (5) normal RA volume and RV end-diastolic area, and (6) normal RV or RA area. Severe TR was considered if the following criteria were fulfilled: (1) VC ≥ 0.7cm, (2) proximal isovelocity surface area radius ≥ 0.9 cm at a Nyquist limit of 30 to 40 cm/sec, (3) central jet area/RA area ratio ≥ 50%, (4) dense TR jet by CW Doppler with triangular or sine wave pattern, (5) systolic flow reversal in the hepatic veins, and (6) dilated right ventricle with preserved function. TR was graded as mild or severe if >50% of available mild or severe parameters were met (all parameters have equal weight). If ≤50% of signs of mild or severe TR were present, VC diameter, effective regurgitant orifice area, and TR

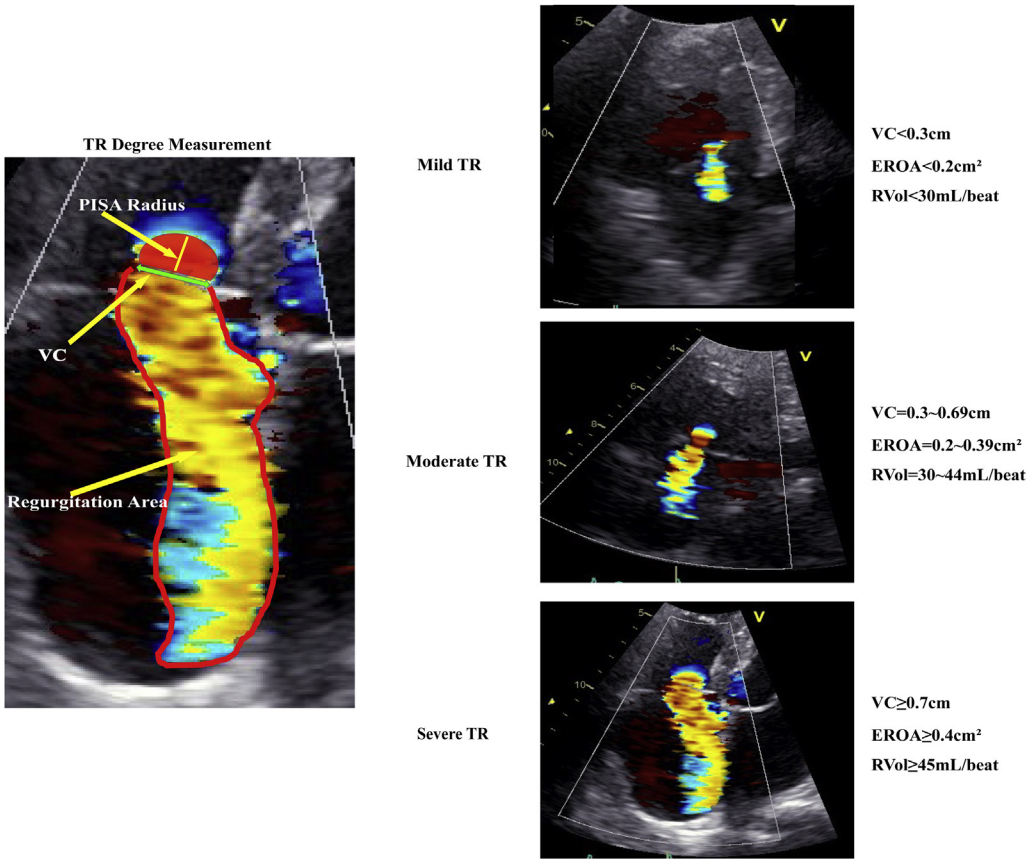


Figure 2 Echocardiographic example of mild, moderate, and severe pacing-induced TR. *EROA*, Effective regurgitant orifice area; *PISA*, proximal isovelocity surface area; *RVol*, regurgitant volume.

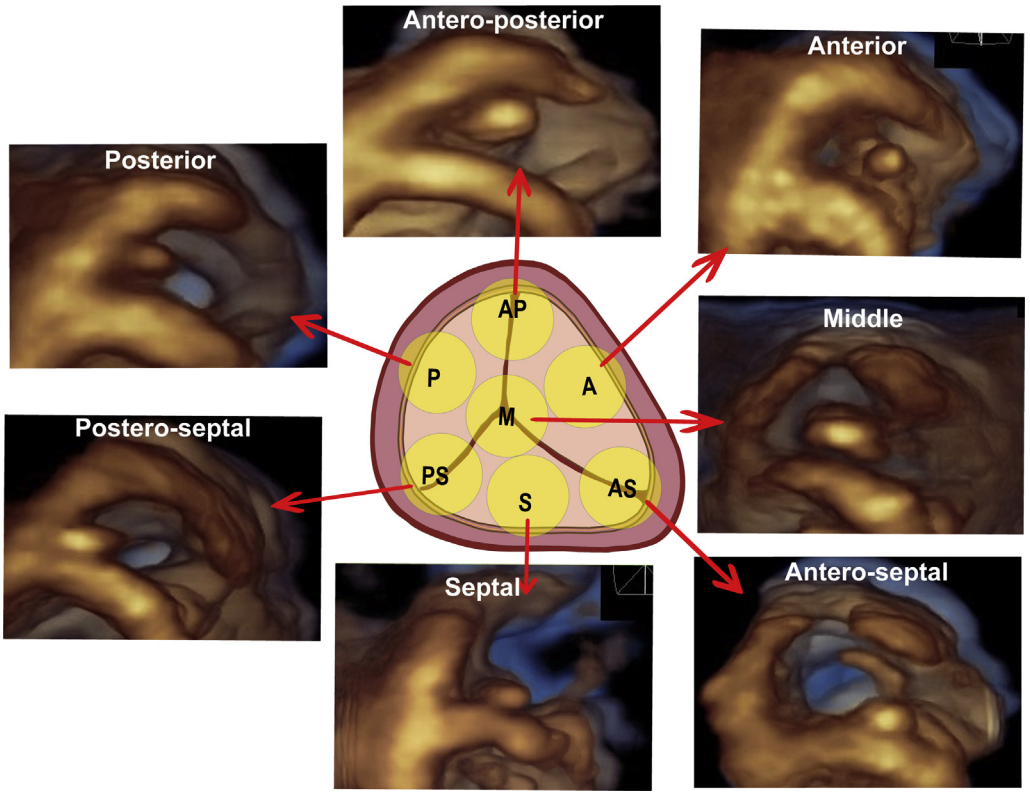


Figure 3 Three-dimensional echocardiography of the pacing leads in relation to the TV.

volume were considered, and severity was determined by the measurement of the three factors.[17] Examples of mild, moderate, and severe TR following PPM implantation are shown in Figure 2.

Three-Dimensional Transthoracic Echocardiography

The details of image acquisition of the TV using 3DE were described in our previous work.[18] In brief, real-time three-dimensional echocardiographic data of the TV were acquired from the apical four-chamber view using a 4V probe (BT 11; GE Vingmed Ultrasound) with electrocardiographic gating over four consecutive cardiac cycles during a single breath hold to maximize temporal resolution. Full-volume imaging was performed in the RV-focused view, and the horizontal line was aligned at the level of the TV cusp in apical four-chamber views, and the central axis of the pyramidal screen was aligned with the RV long axis. The image box height and width were optimized to enclose the TV in zoom mode. The image was subsequently cropped and orientated to visualize the TV leaflet in the en face view. Finally, the TV was oriented such that the septum was in the 6 o'clock position, in accordance with current recommendations.[19]

Device Lead Position Relative to the TV Leaflets

Pacemaker lead position was described as anterior, posterior, or septal if it impinged the respective TV leaflets. The commissure position was defined when the lead was located between two leaflets and was named accordingly: anteroseptal, posteroseptal, or anteroposterior. The pacemaker lead was described to be in the middle position if it passed through the TV without interfering with leaflet motion and not in the commissure position.[5,6] Three-dimensional echocardiographic examples of each position are depicted in Figure 3.

Statistical Analysis

Continuous variables are expressed as mean ± SD and categorical variables as numbers and percentages. Categorical variables are presented as frequencies and percentages, and the χ^2 test was used to test the association between two categorical variables. Comparisons of clinical parameters and the echocardiographic parameters between RVA and non-RVA pacing groups were performed using two-tailed unpaired Student's t test. Binary logistic regression models were used to assess clinical factors associated with worsening of TR (defined as increased TR severity of at least one grade after implantation compared with preimplantation), and variables with P values $<.10$ in univariate regression were included. Intraobserver and interobserver variabilities were assessed using the method described by Bland and Altman and intraclass correlation coefficients from 20 randomly selected patients. The randomly selected group was further used to assess interreader agreement in the evaluation of lead position on three-dimensional echocardiographic images by two experienced independent observers. All statistical analyses were performed using SPSS for Windows version 25.0 (SPSS, Chicago, IL). A two-sided P value $< .05$ was considered to indicate statistical significance.

RESULTS

The baseline characteristics of the study population are shown in Table 1. The average age at the time of PPM implantation was

Table 1 Baseline characteristics of the study population

Variables	Total (*N* = 284)	RVA pacing (*n* = 132)	Non-RVA pacing (*n* = 152)	*P*
Age, y	72 ± 11	73 ± 9	71 ± 12	.03
Sex, male	151 (53.2)	69 (52.3)	82 (53.9)	.78
Time from echocardiography to implantation, mo	5 ± 11	5 ± 10	5 ± 11	.69
Time from implantation to echocardiography, mo	55 ± 38	69 ± 43	43 ± 27	<.01
HTN	207 (72.9)	102 (77.3)	105 (69.1)	.12
Hyperlipidemia	113 (39.8)	55 (41.7)	58 (38.2)	.55
DM	106 (37.3)	51 (38.6)	55 (36.2)	.67
Smoking	66 (23.2)	29 (22.0)	37 (24.3)	.64
IHD	93 (32.7)	42 (31.8)	51 (33.6)	.76
DCM	4 (1.4)	1 (0.8)	3 (2.0)	.39
HCM	6 (2.1)	5 (3.8)	1 (0.7)	.07
CHF	31 (10.9)	15 (11.4)	16 (10.5)	.82
Pre-AF	104 (36.6)	54 (40.9)	50 (32.9)	.17
SSS	111 (39.1)	59 (44.7)	52 (34.2)	.07
AVB	116 (40.8)	46 (34.8)	70 (46.1)	.05
Preimplantation LVEF, %	62.5 ± 8.2	62.8 ± 8.3	61.7 ± 9.9	.31
Post-AF	125 (44.0)	64 (48.5)	61 (40.1)	.16
Vp% > 90%	128 (45.1)	51 (38.6)	77 (50.7)	.04
DDDR	252 (88.7)	121 (91.7)	131 (86.2)	.14
VVIR	32 (11.3)	11 (8.3)	21 (13.8)	.14
Left-side chest pocket	282 (99.3)	132 (100.0)	150 (98.7)	.16
TV passage angle, deg	7.2 ± 33.9	−23.2 ± 19.5	33.6 ± 17.7	<.01
Impinge posterior leaflet	33 (11.6)	21 (15.9)	12 (7.9)	.04
Postechocardiography parameters				
QRS duration, msec	139.8 ± 21.3	150.3 ± 18.2	130.6 ± 19.6	<.01
RVEDA, cm^2	15.4 ± 4.1	15.2 ± 4.0	15.5 ± 4.3	.60
RVESA, cm^2	7.3 ± 2.5	8.0 ± 2.6	7.4 ± 2.7	.63
RVFAC, %	51 ± 11	51 ± 11	51 ± 11	.61
RA area, cm^2	19.0 ± 6.2	19.7 ± 6.3	18.4 ± 6.0	.07
Tricuspid annular diameter, cm	3.3 ± 0.7	3.4 ± 0.7	3.2 ± 0.7	.03
Systolic reversal of hepatic vein flow	95 (33.5)	54 (40.9)	41 (27.0)	.01
Triangular CW of sine wave pattern	85 (29.9)	41 (31.1)	44 (28.9)	.70
Dense CW	128 (45.1)	72 (54.5)	56 (36.8)	<.01
TR velocity, m/sec	2.5 ± 0.6	2.5 ± 0.6	2.4 ± 0.6	.07
LVEDV, mL	74.9 ± 28.2	69.8 ± 25.1	79.3 ± 30.0	<.01
LVESV, mL	29.3 ± 17.5	26.8 ± 14.0	31.5 ± 19.9	.03
LVEF, %	62.3 ± 9.2	62.8 ± 8.3	61.7 ± 9.9	.31
Jet area, cm^2	6.1 ± 5.1	7.1 ± 5.4	5.2 ± 4.6	<.01
Jet area/RA ratio, %	31 ± 23	35 ± 23	27 ± 23	.01
VC width, cm	0.6 ± 0.4	0.6 ± 0.4	0.5 ± 0.4	<.01
PISA radius, cm	0.6 ± 0.3	0.6 ± 0.3	0.5 ± 0.3	<.01
EROA, cm^2	0.4 ± 0.4	0.5 ± 0.5	0.3 ± 0.4	<.01
RVol, mL/beat	37 ± 38	44 ± 40	32 ± 35	<.01
Mild TR	138 (48.6)	48 (36.4)	90 (59.2)	<.01
Moderate TR	57 (20.1)	34 (25.8)	23 (15.1)	.03
Severe TR	89 (31.3)	50 (37.9)	39 (25.7)	.03
Central jet	201 (70.8)	94 (71.2)	107 (70.4)	.59
Eccentric jet	53 (18.7)	27 (20.5)	26 (17.1)	.59

AVB, Advanced atrioventricular block; *CHF*, congestive heart failure; *DCM*, dilated cardiomyopathy; *DDDR*, dual-chamber rate-adaptive pacemaker; *DM*, diabetes mellitus; *EROA*, effective regurgitation orifice area; *HCM*, hypertrophic cardiomyopathy; *HTN*, hypertension; *IHD*, ischemic heart disease; *PISA*, proximal isovelocity surface area; *RVEDA*, RV end-diastolic area; *RVESA*, RV end-systolic area; *RVFAC*, RV fractional area change; *RVol*, regurgitant volume; *RVSP*, RV systolic pressure; *SSS*, sick sinus syndrome; *TAPSE*, tricuspid annular plane systolic excursion; *VVIR*, single-chamber rate-adaptive pacing pacemaker.
Data are expressed as mean ± SD or number (percentage).

72 years, and about half were men. About one third of patients had AF at baseline, a figure that increased to >44% at follow-up. Most patients received DDDR pacemakers, with the device implanted on the left side of the chest wall. Table 1 also shows the baseline characteristics of patients with RVA and non-RVA pacing. Pacing duration was shorter in the non-RVA group than the RVA group, and advanced atrioventricular block as the indication for PPM implantation was more common in the non-RVA than the RVA group.

TR Severity in RVA and Non-RVA Pacing

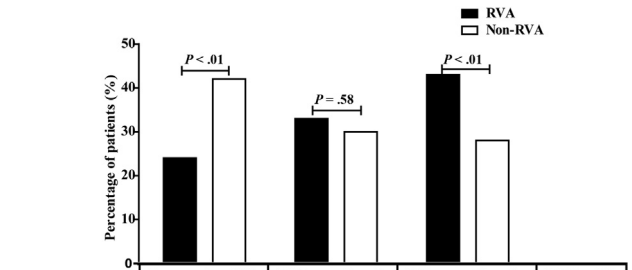
Before pacemaker implantation, the prevalence of no to mild TR (86.8% vs 87.9%, $P = .79$) and moderate TR (13.2% vs 12.1%, $P = .79$) was similar in the non-RVA and RVA groups. Following pacemaker implantation, the prevalence of moderate (25.8% vs 15.1%, $P = .03$) and severe (37.9% vs. 25.7%, $P = .03$) TR became higher, while that of no to mild TR was lower (36.4% vs 59.2%, $P < .01$) in patients with RVA pacing compared with non-RVA pacing. The numbers of patients in the RVA and non-RVA pacing groups with no worsening of TR, TR increase of at least one grade only, and TR increase of at least two grades are shown in Figure 4. Importantly, RVA pacing was associated with an increase in TR severity of at least one grade ($n = 100$ [75.8%] vs $n = 88$ [57.9%], $P < .01$) and at least two grades ($n = 56$ [42.4%] vs $n = 42$ [27.6%], $P < .01$) compared with non-RVA pacing after PPM implantation. Multivariate analysis demonstrated that pacing duration, Vp% > 90%, and RVA pacing were independently associated with worsening of TR severity (Supplemental Table 1).

Lead Position across the TV in Relation to TR Severity

As shown in Figure 5, lead impingement was associated with progressive worsening of TR severity by at least two grades in 55.5% compared with either the middle position (14.5%, $P < .01$) or the commissural position (22.3%, $P < .01$). Conversely, patients with pacing leads in the middle and commissural positions were most likely to remain free of worsening of TR severity of at least two grades compared with those with lead impingement (85.5% and 77.7% vs 44.5%, $P < .01$; Figure 5).

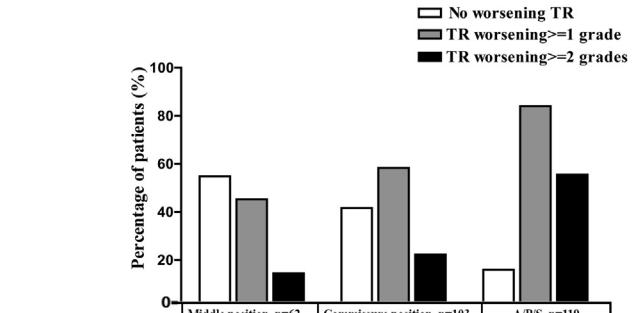
Lead Position across the TV in RVA and Non-RVA Pacing

Lead impingement against one of the leaflets occurred in 119 patients (41.9%; anterior, $n = 3.5\%$; posterior, $n = 11.6\%$; septal, $n = 26.8\%$) and through the middle position in 62 (21.8%). The pacing lead in the remaining 103 patients (36.3%) was located at the commissural position of the TV (anteroseptal, 18%; posteroseptal, 12%; anteroposterior, 6.3%). Furthermore, the pacemaker lead position across the TV was significantly different between patients with RVA and non-RVA pacing (Figure 6). The most common lead passage position was middle for non-RVA versus RVA pacing, whereas it was most common for the RVA lead to impinge on the posterior leaflet. There was no difference between leads in the commissural position in the RVA and non-RVA groups. Nonetheless, the lead position at the posteroseptal commissure was more common in RVA than non-RVA pacing, whereas lead position at the anteroseptal commissure was more common in non-RVA than RVA pacing. Thus, the non-RVA pacing lead was more likely to be sited in the middle or anteroseptal position, and the RVA pacing lead was more likely to be in the posterior or posteroseptal position. Pacing lead in the posterior position was associated with a higher prevalence of severe TR compared with the middle position (57.6% vs 9.7%, $P < .01$), whereas the prevalence of severe TR was similar when the lead position was in the posteroseptal and anteroseptal commissures (8.8% vs 15.7%, $P = .36$).



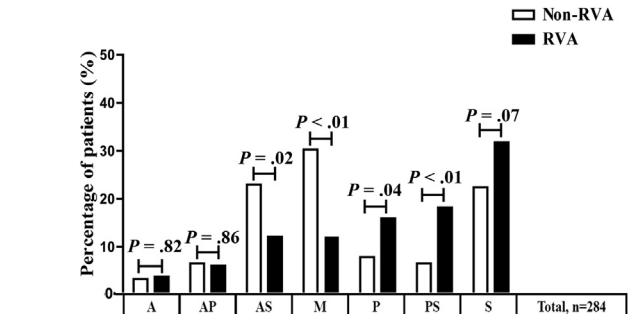
	No worsening of TR, n=96	TR increase 1 grade only, n=90	TR increase ≥2 grades, n=98	Total, n=284
RVA, n (%)	32(24.2)	44(33.4)	56(42.4)	132(100)
Non-RVA, n (%)	64(42.1)	46(30.3)	42(27.6)	152(100)

Figure 4 Change in TR degree following pacemaker implantation in the RVA pacing and non-RVA pacing groups.



	Middle position, n=62	Commissure position, n=103	A/P/S, n=119
No worsening of TR, %	54.8	41.7	16.0
TR increase ≥1 grade, %	45.2	58.3	84.0
TR increase ≥2 grades, %	14.5	22.3	55.5

Figure 5 Change in TR degree in relation to different pacing lead positions across the TV. *A*, Anterior; *P*, posterior; *S*, septal.



	A	AP	AS	M	P	PS	S	Total, n=284
RVA, %	3.8	6.1	12.1	12.1	15.9	18.2	31.8	132
Non-RVA, %	3.3	6.6	23.0	30.3	7.9	6.6	22.4	152

Figure 6 Pacing lead position across the TV in the RVA pacing and non-RVA pacing groups. *A*, anterior; *AP*, anteroposterior; *AS*, anteroseptal; *M*, middle; *P*, posterior; *PS*, posteroseptal.

Analysis of Lead Passage Angle across the TV in RVA versus Non-RVA Pacing

The mean lead passage angle across the TV was −23.2° (range, −42.7° to 3.6°) versus 33.6° (range, 16.0° to 51.3°) in RVA versus

non-RVA lead passage, respectively. The prevalence of lead across the middle position and of impinging on the posterior leaflet as a function of various degrees is shown in Supplemental Table 2. An angle of −45° to 45° was associated with the highest chance of the lead's being across the middle, whereas an angle of −15° to 15° was associated with least chance of the lead's impinging on the posterior leaflet. As a result, an angle of −15° to 15° was associated with the highest chance of lead passage through the middle position (14.8% to 17.6 %) and the least chance at the posterior position (4.2% to 6.7%).

Contribution of Different Multivariate Predictors to the Incidence of TR

In this cohort, RVA pacing in conjunction with Vp% > 90% was associated with severe TR in 24.6%, compared with 17.6% for RVA pacing only and 15.1% for Vp% > 90% only. The risk for progressive worsening of TR was also highest in those with RVA pacing in conjunction with Vp% > 90% (54.6%) compared with those with RVA pacing only (35.2%) or Vp% > 90% only (33.1%). A non-RVA pacing site in conjunction with lack of pacing dependency was associated with the least chance of severe TR (6.7%) and worsening of TR (11.3%).

Intraobserver and Interobserver Variability

Intraobserver and interobserver variability is shown in Supplemental Table 3. Intraobserver and interobserver variability was acceptable for RV parameters, assessment of the severity of TR, and lead passage angle. Two independent observers agreed on device-lead location in 18 of 20 cases (90%). Disagreements were between septal and posteroseptal positions (one case) and between posteroseptal and posterior positions (one case).

DISCUSSION

The present study demonstrates that PPM-induced TR is common and more prevalent in patients with RVA pacing than in those with non-RVA pacing. Three-dimensional echocardiography demonstrated that lead impingement was associated with progressive worsening of TR compared with either middle or commissural passage. Furthermore, we revealed that the pattern of lead-leaflet interference differed for the two types of pacing; lead impingement on the posterior leaflet was more common in patients with RVA pacing. In the same context, lead in the middle position of the TV was more common in non-RVA pacing. A TV lead passage angle of −15° to 15°, dictated by the site of lead attachment, was associated with minimal risk for TR. This differential lead-leaflet interference may explain the higher prevalence of TR with RVA pacing than non-RVA pacing.

Previous studies have suggested that non-RVA pacing may lead to a narrower QRS complex and therefore more physiological ventricular activation, less mechanical and electrical dyssynchrony, reduced myocardial perfusion defect, and preservation of left ventricular function.[7-10] Nonetheless, the effect of RV pacing site in relation to pacing-induced TR has not been confirmed. In a randomized prospective trial comparing pacing leads in the RV apex, non–RV apex, and coronary sinus, neither pacing lead position nor lead diameter was related to TR development 12 months following implantation.[20] In a substudy of the Protection of Left Ventricular Function During Right Ventricular Pacing Study, 145 patients were randomized to receive RVA pacing ($n = 76$) or non-RVA pacing ($n = 69$).[21] RV pacing worsened RV function or TR severity over 2 years but was not affected by the pacing site. In contrast, a prior study demonstrated that RVA pacing was associated with worsening of TR severity compared with non-RVA pacing in patients with AF following atrioventricular nodal ablation.[22] This observation is consistent with another study of 382 patients in which RVA pacing, not non-RVA pacing, was associated with worsening TR severity.[23] The discrepancy of these results could be due to the heterogeneity of device types (some included implantable cardioverter-defibrillators) and/or variable duration between device implantation and echocardiographic evaluation. Furthermore, the method of assessment of TR severity was not consistent among studies: some were based on a visual scale rather than semiquantitative or quantitative assessment.[17]

Pacing-induced TR can occur immediately after PPM implantation[23] but is more frequently seen later.[2] One of the reasons for late TR is the gradual fibrosis at the lead-tissue interface, leading to adherence of the TV apparatus, reported in 34% of patients with pacing-related severe TR.[4] The longer duration of follow-up in this study allowed adequate time to show the potential differences in pacing-induced TR between RVA pacing and non-RVA pacing. Likely, electrical dyssynchrony induced by either AF or RV pacing would further worsen TR in addition to the mechanical effect of the pacing site on the TV itself. Prior studies have also consistently demonstrated that the burden of pacing poses an increased risk for heart failure–related mortality.[24,25] The present study extends this observation and provides evidence that high dependency on RV pacing was related to worsening of TR. This is not surprising, as the duration of dyssynchronized pacing will result in asymmetry of myocardial contraction and will lead to ventricular enlargement and consequent interference with RV function and tricuspid annular dilatation. In the presence of RVA pacing, electrical dyssynchrony will be worse, whereas a non-RVA site may mitigate this to some extent.

Mechanism of TR Induced by RV Pacing Leads

With the advent of 3DE, the route of the pacing lead across the TV can be determined, and studies have shown that the lead-leaflet interference affects the degree of TR.[1,5,6] We report the novel observation that lead-leaflet interaction differs between RVA and non-RVA pacing. The preferential lead position across the middle position of the TV may thus result in a lower prevalence of TR in patients with non-RVA pacing. Alternatively, RVA pacing is associated with preferential lead impingement on the posterior leaflets, with a higher prevalence of TR. Indeed, lead impingement on the posterior leaflet with consequent higher degree of TR was also demonstrated by Seo *et al.*[1] One of the possible explanations for the preferential lead impingement on the posterior leaflet in patients with RVA pacing is the negative angle of attachment that induces the lead to direct toward the posterior leaflet, whereas non-RVA pacing is positive and is away from the posterior leaflet, as shown in our TV lead passage angle analysis (Figure 1). An angle of attachment of lead passage across the TV between −15° and 15° was also associated with middle passage, which is favored by a non-RVA site.

Clinical Implications

Pacing-induced TR has been shown to increase mortality 1.7- to 2.1-fold.[26,27] Methods to reduce the occurrence of this complication are thus essential to improve the clinical outcomes of patients who require PPM implantation. We have demonstrated that non-RVA lead positioning that results in a higher chance of central passage of the lead through the TV can minimize severe TR and progression

of TR over time. This is a risk factor that is modifiable at the time of implantation. Avoidance of high Vp% to reduce ventricular dyssynchrony is also important. Nevertheless, future progression (27.6%) of TR increases of at least two grades even in a non-RVA site lead remained significant. Indeed, the Protection of Left Ventricular Function During Right Ventricular Pacing Study demonstrated that although left ventricular asynchrony was more frequent in patients with RVA pacing than in those with non-RVA pacing, the reductions in left ventricular ejection fraction were similar in the two groups.[14] The deterioration of left ventricular ejection fraction may explain the increased TR in patients with non-RVA pacing. Furthermore, although with a lower frequency, lead impingement at the posterior leaflet is still present in patients with non-RVA pacing (7.9%) compared with RVA pacing (15.9%). These factors may thus explain that non-RVA pacing may reduce, but is not able to completely eliminate, the risk for pacing-induced TR. With the advances in probe design, image quality, and time of image acquisition, it is theoretically possible to perform periprocedural 3DE during PPM implantation. The potential benefit of periprocedural 3DE to guide the lead route across the TV to prevent TR should be thoroughly evaluated in a future randomized study. To minimize TR and prevent its development, the reduction of interventricular dyssynchrony by non-RVA pacing may prevent adverse ventricular remodeling and thus reduce annular dilatation and subsequent TR. This hypothesis was tested by a prior study that showed that para-Hisian pacing reduced TR, while RVA pacing increased TR severity.[22] The use of leadless pacing without mechanical TV interference has been suggested to minimize TR.[28] Nonetheless, a recent study demonstrated that the prevalence of pacing-induced TR was similar between leadless pacing and conventional pacemaker.[29] The possible explanation includes TV damage during implantation, the ongoing mechanical impact of the device on the TV and subvalvular apparatus, and pacing-induced RV dyssynchrony and further highlights that the mechanism of pacing-induced TR is multifactorial. The present study demonstrates that different pacing sites contribute to variable lead-leaflet interactions; future studies are warranted to evaluate methods to minimize the development of pacing-induced TR.

Limitations

One of the limitations of this study is its retrospective nature, and the present results will need to be validated in future prospective studies. A multiparametric two-dimensional approach was used to assess the degree of TR, as recommended in current guidelines; nonetheless, the device lead might interfere with the visualization of regurgitant jet and may affect the accuracy of the assessment. Future studies using 3DE-derived proximal isovelocity surface area may better quantify TR severity.[30] Angiographic mapping was not performed during PPM implantation, and the exact lead location of non-RVA pacing (septal or outflow tract) was not systematically documented. Instead, we used postoperative chest radiography to view the final position of the lead as a surrogate marker, which was also used in the prior study.[13] With newer generations of PPMs, the use of magnetic resonance imaging to evaluate lead-leaflet relation may provide additional information complementary to 3DE.[31] Furthermore, myocardial dyssynchrony, a potential mechanism to develop pacing-induced TR, was not assessed in our study population. Future studies are thus required to evaluate whether the differential myocardial dyssynchrony between RVA and non-RVA pacing contributes to the development of TR. The decision of RVA versus non-RVA pacing and the landing position of the lead was operator dependent. A randomized study to compare RVA versus non-RVA pacing is thus required to further confirm our findings. In the present study, 3DE was focused mainly on the en face assessment of the TV to evaluate lead-leaflet interference. Future studies with additional imaging fields should be considered to evaluate the passing angle of the lead across the TV valve assessed on 3DE. Finally, the prognostic value of TR severity between RVA and non-RVA pacing was not determined in the present study. Our sample size was small, and thus we could not determine the relative contributions of posterior leaflet impingement versus RVA pacing in terms of worsening of TR, which requires elucidation in a future study with a larger population.

CONCLUSION

The present study demonstrated that RV pacing is associated with the progression of TR over time. This occurred with a higher prevalence in patients with RVA pacing than in those with non-RVA pacing. Importantly, preferential lead impingement in RVA pacing was a likely mechanism, as demonstrated by 3DE. Implantation at a non-RVA position is a potential method to avoid the development of and progression to severe TR over time.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2020.06.014.

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