



Effect of right ventricular pacing on left ventricular systolic function in patients with Tetralogy of Fallot



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ABSTRACT

Background: Prevalence of pacemaker-induced cardiomyopathy (PICM) in adults with congenital heart disease is unknown. Tetralogy of Fallot (TOF) is a common diagnosis in the adult congenital heart disease population, and the purpose of this study was to determine association between frequent right ventricular (RV) pacing and temporal decrease in left ventricular ejection fraction (LVEF) from pre-implantation to 2-years post-implantation (LVEF_{post-pre}) in TOF patients.

Methods: We studied TOF patients that received RV leads only (N = 51) and a reference group of 7 patients with atrial pacing or biventricular pacing. We defined PICM as a $\geq 10\%$ decrease in LVEF resulting in LVEF $< 50\%$. Linear regression was used to assess relationship between frequent RV pacing ($\leq 20\%$, 21–40%, $> 40\%$) and LVEF_{post-pre}.

Results: PICM occurred in 2 (4%) of 51 patients in RV pacing group. LVEF_{post-pre} was +3% (95% confidence interval [CI] 0% to +5%) in the reference group and –4% (95% CI –11% to +2%) in RV pacing group. No significant difference occurred in LVEF_{post-pre} between the reference group (LVEF_{post-pre} +3%) vs RV pacing $\leq 20\%$ (LVEF_{post-pre} +1%) vs RV pacing 21–40% (LVEF_{post-pre} –3%) vs RV pacing $> 40\%$ (LVEF_{post-pre} –5%), $p = 0.318$. There was also no association between frequent RV pacing and LVEF_{post-pre}, $R^2 = 0.307$, $p = 0.10$.

Conclusion: PICM occurred in 4% of TOF patients receiving RV pacing, and there was no association between frequent RV pacing and temporal decline in LVEF. Further studies are required to determine the long-term impact of RV pacing in the TOF population, and explore optimal treatment strategies.

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1. Introduction

Chronic right ventricular (RV) pacing results in electromechanical dyssynchrony and can lead to pacemaker-induced cardiomyopathy (PICM) characterized by left ventricular (LV) systolic dysfunction and heart failure [1–3]. The prevalence of PICM ranges from 12% to 20%, and the risk factors for PICM include frequent RV pacing, QRS duration, preexisting left bundle branch block, and LV systolic dysfunction prior to pacemaker implantation [1,2,4,5]. Biventricular pacing is effective for preventing and reversing PICM, and is endorsed by the practice guidelines for selected cases [1–4,6].

Although some studies have reported hemodynamic and symptomatic benefits from biventricular pacing in patients with congenital heart disease [7,8], the prevalence of PICM in this population is unknown. Considering the heterogeneity of the congenital heart disease population, we expect that the risk of PICM will vary by the type of congenital heart lesion. Tetralogy of Fallot (TOF) is the most common moderate/complex congenital heart lesion in the adult congenital heart disease population, and 5–10% of TOF patients will require pacemaker implantation in their lifetime [9,10]. RV pacing-induced left bundle branch block and electromechanical dyssynchrony is one of the proposed pathophysiologic mechanism leading to PICM [1–3]. TOF patients, on the other hand, have right bundle branch block, and their response to pacing may be different from that of other patients without underlying bundle branch block [11,12]. Since PICM is associated with poor prognosis and biventricular pacing can prevent PICM and improve outcomes based on data from patients with acquired heart disease [1–4,6], the lack of similar data in the TOF population constitutes an important knowledge gap. Here, we studied the association between RV pacing and temporal decrease in left

Abbreviations: TOF, Tetralogy of Fallot; PICM, pacemaker-induced cardiomyopathy; RV, right ventricle; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RVSP, right ventricular systolic pressure; RA, right atrium.

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ventricular ejection fraction (LVEF) from pre-implantation to 2-years post implantation in TOF patients.

2. Methods

2.1. Patient selection

The MACHD (**Mayo Adult Congenital Heart Disease**) database was queried for patients (age ≥ 18 years) with repaired TOF that received endocardial pacemakers at Mayo Clinic Rochester, Minnesota from January 1, 1990 through December 31, 2017. We excluded patients without echocardiograms prior to pacemaker implantation, and patients that had surgical and/or transcatheter interventions between the echocardiogram pre- and post- pacemaker implantation. These patients were divided into 3 groups based on the locations of the pacemaker leads. The patients that received dual chamber pacemakers (right atrial [RA] and RV leads) and the patients that received only RV leads were classified as the RV pacing group, and these patients comprised the study cohort and were used for all subsequent analysis. The patients that received isolated RA leads were classified as the atrial pacing group, and the patients that received dual chamber pacemakers plus a coronary sinus lead were classified as the biventricular pacing group. The atrial pacing and the biventricular pacing groups were used as the reference group. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization.

2.2. Study endpoints and definitions

The primary study objective was to determine the prevalence of PICM in patients with chronic RV pacing, and the association between frequent RV pacing and temporal reduction in LVEF. The secondary objective was to determine if frequent RV pacing was associated with temporal change in LV stroke volume, LV end-systolic dimension (LVESD), and RV systolic pressure (RVSP).

LVEF_{pre} was based on the last echocardiogram prior to pacemaker implantation and LVEF_{post} was based on the echocardiogram performed 2 years (± 3 months) post pacemaker implantation. Temporal change in LVEF was calculated as LVEF in the post-implantation echocardiogram minus LVEF in the pre-implantation echocardiogram (LVEF_{post-pre}). Temporal changes in LV stroke volume, LVESD, and RVSP were also assessed as the difference in the indices obtained from echocardiogram performed pre-implantation and post-implantation (Echocardiogram_{post-pre}). We defined PICM as a $\geq 10\%$ decrease in LVEF resulting in LVEF $< 50\%$ similar to previous studies [1,2].

2.3. Pacemaker data

Procedure/operation notes, clinic notes, and reports of device interrogation were reviewed. The pre-implantation electrocardiograms were reviewed to determine rhythm and native (non-paced) QRS duration. All device interrogation reports were reviewed to determine pacemaker settings and frequency of RV pacing. In patients with more than one device interrogation, we used the device interrogation report with the highest RV pacing frequency for categorization. In order to assess the effect of frequent RV pacing on LVEF, we divided the patients with RV pacing into 3 subgroups based on the frequency of RV pacing: $\leq 20\%$, 21–40%, and $> 40\%$ [1,2]. The temporal change in LVEF (LVEF_{post-pre}) was compared between the different subgroups of RV pacing and the reference group of patients with atrial or biventricular pacing.

2.4. Echocardiography

Transthoracic echocardiography was performed according to standard American Society of Echocardiography guidelines [13]. LVESD was assessed from the left parasternal long axis window using 2-D echocardiography [13]. Doppler-derived LV stroke volume was assessed using the hydraulic orifice formula (flow rate = cross-sectional area \times flow velocity), and calculated as $0.785 \times (\text{LV outflow tract diameter})^2 \times \text{LV outflow tract time velocity integral}$ [13]. Doppler-derived RVSP was calculated using the Bernoulli equation [13]. Offline measurements and calculations of LVEF, LVESD, LV stroke volume and RVSP were performed by a single observer (R.P), an experienced sonographer that was blinded to the study objectives.

2.5. Statistical analysis

Data are presented as mean \pm standard deviation, median (range) or number (%). First we calculated LVEF_{post-pre} as the difference between pre-implantation and post-implantation values. We compared LVEF_{post-pre} between the reference group (atrial pacing and biventricular pacing groups) and the 3 RV pacing sub-groups ($\leq 20\%$, 21–40%, and $> 40\%$ RV pacing) using analysis of variance (ANOVA). We then performed pairwise comparison between the reference group and each of the RV pacing sub-groups. Linear regression was used to assess the relationship between frequent RV pacing (predictor) and LVEF_{post-pre} (outcome). In the regression model, frequent RV pacing was analyzed as categorical variable ($\leq 20\%$, 21–40% and $> 40\%$). We adjusted for potential predictors and confounders of the relationship between frequent RV pacing and LVEF_{post-pre}, using variables and potential predictors described in previous studies [1,2]. The variables adjusted for in the model were native QRS duration, pre-implantation LVEF, age, pulmonary regurgitation (\geq moderate pulmonary regurgitation vs less regurgitation), and RV systolic dysfunction (\geq moderate RV systolic dysfunction based on echocardiography vs less systolic dysfunction). Prevalence of PICM was calculated as the proportion of patients with a $\geq 10\%$ decrease in LVEF resulting in LVEF $< 50\%$ between pre- and post-implantation of pacemaker.

For the secondary objective, we calculated LV stroke volume_{post-pre}, LVESD_{post-pre}, and RVSP_{post-pre} in the RV pacing group as the difference between pre-implantation and post-implantation values. ANOVA followed by pairwise comparison were used to assess between-group differences in LV stroke volume_{post-pre}, LVESD_{post-pre}, and RVSP_{post-pre}. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP software (version 14.0; SAS Institute Inc, Cary NC).

3. Results

3.1. Baseline characteristics

Out of 66 patients with pacemaker implantations, we excluded 8 (12%) patients that did not have pre-implantation or post-implantation echocardiographic data. Of the remaining 58 patients, 51 (88%) patients were in the RV pacing group and 7 patients (12%) were the reference group (atrial pacing group $n = 4$ and biventricular pacing group $n = 3$). The 51 patients in the RV pacing group comprised the study cohort and their clinical characteristics at the time of pacemaker implantation are shown in Table 1.

3.2. Pacemaker data

The mean age at the time of pacemaker implantation was 37 ± 15 years, and the indications for pacing were sinus node dys-

Table 1
Baseline Characteristics of RV Pacing Group (N = 51).

Age at beginning of study, years	37 ± 15
Male	26 (51%)
Body mass index, kg/m ²	27 ± 7
Body surface area, m ²	1.9 ± 0.4
Age at TOF repair, years	5 (3–11)
Prior palliative shunt	24 (37%)
TOF-pulmonary atresia	13 (26%)
Comorbidities	
Atrial fibrillation	18 (35%)
Atrial flutter/tachycardia	15 (29%)
Hypertension	12 (24%)
Hyperlipidemia	13 (26%)
Coronary artery disease	6 (12%)
Diabetes mellitus	5 (10%)
Laboratory tests	
Hemoglobin, g/dl	14.0 ± 2.6
Creatinine, mg/dl	1.1 ± 0.4
NT-proBNP, pg/ml	271 (122–718)
Medications	
Diuretics	11 (21%)
Beta blockers	8 (16%)
Warfarin	5 (10%)
Aspirin	11 (22%)

TOF: Tetralogy of Fallot; NT-proBNP: N-terminal pro b-type natriuretic peptide.

function in 16 (31%), heart block in 36 (71%) and anti-tachycardia pacing for atrial arrhythmias in 4 (8%); 36 (71%) patients received rate-responsive pacemakers (Table 2). The mean native QRS duration at the time of pacemaker implantation was 141 ± 29 ms and 31 (61%) patients had QRS duration >140 ms.

The pacing modes at the time of pacemaker implantation were single-chamber RV pacing (VVI) in 11 (22%) patients and dual-chamber pacing (DDD) in 40 (78%) patients. The average number of device interrogations between the time of implantation and the 2-year follow-up assessment was 3 ± 1, yielding a total of 156 device interrogation reports. Of the 156 device interrogation reports, maximal RV pacing frequency was ≤20% in 27 (53%) patients, 21–40% in 16 (31%) patients and >40% in 8 (16%) patients. We also assessed RV pacing frequency as an ‘average’ pacing frequency rather than ‘maximal’ RV pacing frequency. Based on average RV pacing frequency, we observed ≤20% in 29 (57%) patients, 21–40% in 15 (29%) patients and >40% in 7 (14%) patients.

3.3. Outcomes

The echocardiographic data pre-implantation (baseline) and post-implantation (2-year follow-up) are shown in Table 3. The

Table 2
Pacemaker Data of RV Pacing Group (N = 51).

Pacing leads	
RV lead only	6 (12%)
RA and RV leads	45 (82%)
Indications	
Sinus node dysfunction	16 (31%)
Heart block	36 (71%)
Atrial arrhythmias/anti-tachycardia pacing	4 (8%)
RA lead sensing threshold (mV)	1.8 ± 0.9
RA lead pacing threshold (V)	0.9 ± 0.4
RA lead impedance (ohms)	361 ± 174
RA pulse width (ms)	0.41 ± 0.05
RV lead sensing threshold (mV)	8.4 ± 5.8
RV lead pacing threshold (V)	1.2 ± 0.8
RV lead impedance (ohms)	381 ± 196
RV pulse width (ms)	0.40 ± 0.04

RA: Right atrium; RV right ventricle.

Table 3
Echocardiographic Data of RV Pacing Group (N = 51).

Echocardiography	Pre-implantation	Post-implantation	p
LVEDD, mm	50 ± 7	52 ± 7	0.304
LVESD, mm	34 ± 7	35 ± 6	0.367
LVEF, %	55 ± 10	52 ± 8	0.208
LVEF < 50%	6 (12%)	9 (18%)	0.402
LV stroke volume index, mL/m ²	48 ± 11	41 ± 8	0.072
Cardiac index, L/min/m ²	2.6 ± 0.5	2.8 ± 0.4	0.384
Heart rate, bpm	54 ± 7	64 ± 4	0.026
RV FAC, %	34 ± 10	36 ± 9	0.241
TAPSE, cm	18 ± 6	19 ± 7	0.361
RV s', cm/s	10 ± 3	9 ± 2	0.414
Tricuspid regurgitation velocity, m/s	3.1 ± 0.7	3.0 ± 0.6	0.766
RVSP, mmHg	46 ± 9	45 ± 6	0.297
≥Moderate tricuspid regurgitation	4 (8%)	6 (12%)	0.733

LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular systolic dimension; LVEF: Left ventricular ejection fraction; RV: right ventricle; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; s': tissue Doppler systolic velocity.

mean LVEF was 55 ± 10%, and 9 (18%) patients had LVEF <50%. The temporal change in LVEF (LVEF_{post-pre}) in the reference group was +3% (95% confidence interval [CI] 0% to +5%) while the LVEF_{post-pre} in RV pacing group was −4% (95% CI −11% to +2%). Table 4 shows the LVEF_{post-pre} for the different RV pacing subgroups. There was no significant difference in LVEF_{post-pre} between the different groups (+3% vs +1% vs −3% vs −5%, p = 0.318), or between the reference group and the different RV pacing subgroups by pairwise comparisons. There was also no significant association between frequent RV pacing and LVEF_{post-pre} both in the univariate (R² = 0.384, p = 0.07) and multivariate (R² = 0.307, p = 0.10) models. Of the 51 patients, 24 (47%) patients had more than one echocardiogram performed after 2 years post pacemaker implantation. Offline image analysis was made by the same observer (K.P) and by one of the authors (A.C.E). The intraobserver and interobserver correlation for LVEF was 0.94 (95% confidence interval 0.90–0.99) and 0.90 (95% confidence interval 0.83–0.95).

The pre- and post-implantation LV stroke volume index, LVESD and RVSP are shown in Table 3. The means LV stroke volume index_{post-pre} was −6 ± 5 mL/m², means LVESD_{post-pre} was 2 ± 4 mm, and means RVSP_{post-pre} was 1 ± 3 mmHg. There were no between-group differences in LV stroke volume index_{post-pre}, LVESD_{post-pre}, and RVSP_{post-pre} for the different RV pacing subgroups. Of the 51 patients, 37 (73%) had NT-proBNP at 2 years post implantation, and the median values was 298 (109–552). The mean difference of NT-proBNP (baseline – follow-up) was 33 (95% confidence interval −16 to 47).

PICM occurred in 2 (4%) patients. One of the patients with PICM was a 43-year old man with pre-implantation and post-implantation LVEF of 55% and 41%. The maximum percentage of RV pacing was 43% in this patient. His beta-blocker was up-titrated and renin-angiotensin-aldosterone system antagonist was initiated. This patient did not have subsequent clinical or echocardiographic follow-up. The second patient was a 48-year old man with pre-implantation and post-implantation LVEF of 50% and 37%. The maximum percentage of RV pacing was 29% in this patient. This patient also had documented non-sustained ventricular tachycardia, and subsequently underwent device upgrade to biventricular pacing with a defibrillator. A follow-up echocardiogram performed at 5 months and 12 months post implantation of biventricular pacing system showed LVEF of 40% at both time points.

Table 4
Temporal change in LV ejection fraction.

Groups	LVEF _{post-pre}	95% CI
Reference group (N = 7)	+3	0 to + 5
≤20% RV pacing (N = 27)	+1	−7 to + 5
21–40% RV pacing (N = 16)	−3	−11 to + 3
>41% RV pacing (N = 8)	−5	−9 to + 5

Reference group: Patients with atrial pacing or biventricular pacing; LVEF_{post-pre}: difference between left ventricular ejection fraction pre- and post-implantation; CI: Confidence interval; RV: Right ventricle.

4. Discussion

In this study of 51 adult TOF patients with RV pacing, the prevalence of PICM was 4% at 2 years post-implantation. Overall the temporal change in LVEF did not differ between patients with RV pacing and the reference group. The prevalence of PICM in adults with congenital heart disease is unknown and as a result we are unable to make a direct comparison between our estimates and previous studies. However data from the pediatric population show that chronic RV pacing is associated with myocyte remodeling and subsequent LV systolic dysfunction [14–16].

The prevalence of PICM in patients with acquired heart disease is 12% to 20% [1,2]. In a retrospective study of 1750 patients with acquired heart disease undergoing pacemaker implantation, PICM occurred in 20% of the patients, and risk factors for PICM were wider native QRS duration, and frequent RV pacing defined as RV pacing greater than 20% [2]. Similar results were also reported in a different study of 823 patients with acquired heart disease showing a PICM prevalence of 12%, and the risk factors for PICM were wider native QRS duration, frequent RV pacing, and LV systolic dysfunction at the time of pacemaker implantation [1]. In comparison to these previous studies, it appears that the prevalence of PICM is lower in the TOF population. We speculate this may be related to differences in the electromechanical characteristics of TOF patients who have preexisting right bundle branch block in contrast to predominance of left bundle branch block in these previous studies. Additionally frequent RV pacing was less common in our cohort as only 16% had RV pacing frequency >40% compared to prior studies where more than one-third of the patients had RV pacing frequency >40% [1,2].

The hemodynamic effects of different configurations RV and biventricular pacing have been studied in animal models and children with congenital heart disease [12,14,17]. In 7 pig models of TOF, RV pacing was associated with acute decreased in LV systolic function as measured by LV dP/dt while biventricular pacing resulted in improvement in electromechanical dyssynchrony and improvement in LV systolic function [17]. A similar observation of biventricular pacing resulting in hemodynamic improvement was reported in small pilot studies of TOF patients [11,17].

4.1. Clinical implication and future direction

Biventricular pacing is associated with hemodynamic and symptomatic improvement in patients with congenital heart disease [7,8]. These studies were conducted in pediatric patients with severe LV dysfunction from different etiologies including dilated cardiomyopathy. The role of biventricular pacing in the prevention and treatment PICM in congenital heart disease patients is unknown. The current study suggests that PICM can occur in patients with repaired TOF but it may not be as common as reported in the acquired heart disease population. Further studies are required to explore the prevalence and risk factors for PICM, as well as the impact of RV pacing in TOF in general.

4.1.1. Limitations

The current study was limited by retrospective study design and small sample size, which prohibited more robust analysis for risk factors of PICM. There were no electro-anatomic mapping data and invasive hemodynamic data at the time of pacemaker implantation, and as a result we are unable to comment on the hemodynamic effects of different RV pacing sites and configurations. There was a limited follow-up of only 2 years, and it is possible that more patients might have developed PICM during long-term follow-up.

4.1.2. Conclusions

PICM occurred in 4% of TOF patients receiving RV pacing, and overall there was no significant association between frequent RV pacing and temporal decline in LVEF. We speculate that the low prevalence of PICM may be related to the fact that electrical dyssynchrony of the RV is initiated by the delayed activation of the RV compared to the LV. As such, RV pacing may help to restore the physiological activation pattern and could be more physiological in TOF. Further mechanistic studies with a larger cohort and longer follow-up are required to validate these findings.

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Appendix A. Supplementary material

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