Pacing Therapy in Children – Repeat Left Ventricular Pacing for Preservation of Ventricular Function –

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Background: The importance of ventricular pacing site in pediatric pacemaker therapy has gradually become recognized. We reviewed our experience with a left ventricular (LV)-prioritized pacing strategy.

Methods and Results: Between 2000 and 2012, 60 patients underwent 76 permanent pacemaker implantations. Eight of the 29 reoperations involved ventricular lead repositioning for pacing-induced ventricular dysfunction. Freedom from ventricular lead failure was 96.3%, 86.8%, and 81.0% at 1, 3, and 5 years, respectively. The independent predictors of ventricular lead failure were age ($P=0.026$) and peak minimal energy threshold within 6 months ($P=0.035$). At the measured points, redo bipolar, steroid-eluting leads had significantly better pacing properties than did redo non-steroid-eluting, screw-in leads ($P=0.0009$ – 0.03). Ventricular lead repositioning was effective in the 5 patients with systemic LV pacing, whereas its efficacy was inconsistent in patients with single-ventricle or systemic right ventricular (RV) pacing. At a median follow-up of 59 months, the 28 patients with LV pacing had preserved ventricular function (LV fraction shortening, 0.34 ± 0.09).

Conclusions: The outcome of this LV-prioritized pacing strategy in pediatric patients was excellent, demonstrating preserved ventricular function. Bipolar, steroid-eluting, epicardial pacing leads achieved good pacing properties, even in reoperation patients. In children with systemic LV and RV pacing-induced ventricular dysfunction, a conversion to LV apex pacing was an attractive alternative to cardiac resynchronization therapy. (*Circ J* 2014; **78**: 2972–2978)

Key Words: Cardiac function; Pacemaker; Pediatrics

Despite the importance of optimal lifelong pacing in children, many controversies exist concerning the pacing strategies used for this age group.^{1–9} A single approach has been impractical, and some specific characteristics, such as patient body size, combined structural heart disease, history of cardiac operation, and preoperative ventricular function, should be taken into consideration. Although right ventricular (RV) pacing has been used for decades in the pediatric age group, reports concerning the adverse effects of RV pacing and the efficacy of left ventricular (LV) pacing have increased.^{1–4,10–17} We encountered a patient with RV pacing-induced LV dysfunction in 2005. Since then, the therapeutic policy has been to maintain LV pacing, even in redo cases. Reports concerning pacemaker reoperations in pediatric patients, however, are especially limited.

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Thus, the aim of this study was to evaluate the influence of pacing site on ventricular function, factors affecting lead longevity, and the strategy for redo pacemaker implantation in pediatric patients.

Methods

Patients

The subjects consisted of 60 consecutive patients who underwent permanent pacemaker implantation between 2000 and 2012 at Kobe Children's Hospital, Japan. The Kobe Children's Institutional Review Board approved this study and granted an informed consent waiver. There were 47 initial pacemaker

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Table 1. Operative Data

Characteristics	Primary PMI (n=47)	Redo-PMI (n=29)
M/F	27/20	9/20
Age at operation (years)	3.3 (0.04–21)	10.2 (0.3–27)
Height (cm)	88 (42–176)	126 (51–164)
Weight (kg)	11.5 (1.8–68)	23.7 (3.4–64)
Surgical approach		
Left thoracotomy	27 (57)	16 (55)
Right thoracotomy	1 (2)	0 (0)
Median sternotomy	13 (28)	6 (21)
Subxiphoidal approach	4 (9)	4 (14)
Transvenous approach	2 (4)	3 (10)
Atrial lead	37	22
4951 (Medtronic; fishhook, unipolar, non-steroid)	16 (43)	8 (36)
4965 (Medtronic; sutured, unipolar, steroid)	2 (5)	2 (9)
4968 (Medtronic; sutured, bipolar, steroid)	16 (43)	11 (50)
Transvenous leads	3 (8)	1 (5)
Ventricular lead	45	26
5071 (Medtronic; screw in, unipolar, non-steroid)	14 (31)	6 (24)
4965 (Medtronic; sutured, unipolar, steroid)	6 (13)	0 (0)
4968 (Medtronic; sutured, bipolar, steroid)	18 (40)	14 (54)
51121 (Greatbath Medical; screw in, bipolar, non-steroid)	5 (11)	2 (8)
1043K (St Jude Medical; screw in, unipolar, non-steroid)	0 (0)	1 (4)
Transvenous lead	2 (4)	3 (12)
Ventricular pacing site		
Left ventricle	27 (60)	16 (62)
Right ventricle	8 (18)	9 (35)
Single ventricle	10 (22)	1 (4)
Pacing mode		
AAI/R	4 (9)	0 (0)
VVI/R	11 (23)	7 (24)
DDD/R	32 (68)	22 (76)

Data given as median (range) or n (%). AAI, atrial demand mode; DDD, atrioventricular synchronized pacing; PMI, permanent pacemaker implantation; VVI, ventricular demand mode.

implantation operations and 29 operations for system reimplantation or system revision; patients who underwent only generator replacement were excluded. All patient medical records were reviewed retrospectively. Arrhythmia diagnosis included congenital atrioventricular block (AVB, n=17), acquired AVB (n=33), and sinus node dysfunction (n=10). Structural congenital heart disease was present in 46 patients, including ventricular septal defect (n=6), atrioventricular septal defect (n=5), tetralogy of Fallot (n=3), pulmonary atresia with ventricular septal defect (n=3), transposition of the great arteries (n=3), congenitally corrected transposition of the great arteries (n=3), single LV (n=3), single RV (n=7), and single ventricle (SV) with heterotaxy syndrome (n=5). Among the 29 redo patients, the major indications for pacing system replacement were ventricular dysfunction (n=8), lead fracture (n=7), high threshold (n=6), upgrade to dual-chamber pacing (n=3), infection (n=2), insulation break (n=1), overstretch (n=1), and phrenic stimulation (n=1).

Surgical Technique

The operative data, including patient demographics, pacing leads used in the study, ventricular pacing site, and pacing mode are listed in [Table 1](#). The preferential approach involved a left thoracotomy through the fourth intercostal space. In re-

peat thoracotomy cases, intercostal incision (usually through the fifth intercostal space) was decided on the basis of chest radiography. To improve the contact between the electrode and the myocardium, a small area of scar tissue on the epicardium was dissected, as needed. When a bipolar, steroid-eluting lead (4968; Medtronic, Minneapolis, MN, USA) was implanted, a negative electrode was usually sutured to the LV apex and a reference electrode was sutured to the RV anterior wall or LV lateral wall. For a patient undergoing lead reimplantation, old leads were extracted, if possible. A median sternotomy approach was used for patients with concomitant cardiac procedures. A subxiphoidal approach was mainly used for RV pacing in an emergency setting or for the addition of a right atrial lead during upgrade to DDD dual-chamber (DDD) pacing. In this approach, a lower partial sternotomy was added, as needed. In all epicardial pacing patients, except small neonates, the pulse generator was implanted in the abdominal rectus sheath; a subrectus pocket was created for small neonates. A transvenous approach was used for grown patients or for those with previous epicardial system infection.

Follow-up

Atrial and ventricular lead status were obtained at implantation, 1 month after implantation, and at 6-month intervals

Figure 1. Kaplan-Meier survival after first pacemaker implantation, stratified by cardiac anatomy. BV, biventricular heart; PMI, permanent pacemaker implantation; SHD, structural heart disease; SV, single ventricle.

Characteristic	HR	95% CI	P-value
Univariate			
Age (years)	0.879	0.739–0.998	0.028
Structural heart disease	1.239	0.350–5.778	0.753
Redo	0.740	0.193–2.459	0.628
Sutured	0.460	0.100–1.615	0.234
Bipolar	0.256	0.039–0.998	0.0497
Pacing threshold at operation (V)	5.195	0.874–31.904	0.07
Peak MET within 6 months (μ J)	1.046	1.015–1.074	0.052
Multivariate			
Age (years)	0.879	0.742–0.987	0.026
Peak MET within 6 months (μ J)	1.036	1.003–1.071	0.035

CI, confidence interval; HR, hazard ratio; MET, minimal energy threshold.

thereafter. For the purpose of ventricular lead survival analysis, lead failure was defined as the need for replacement based on the presence of an exit block, increased pacing or sensing thresholds, fracture or insulation break, overstretch, phrenic stimulation, or infection.

Ventricular lead revision for ventricular dysfunction was excluded from the end-point, if its pacing and sensing status were acceptable. Lead survival analysis was performed for all ventricular leads except in early deaths and patients with atrial demand mode ($n=60$). To compare lead status, the minimal energy threshold (MET) was calculated according to the following equation: $MET (\mu J) = [\text{voltage (V)}^2 \times \text{pulse width (ms)} \times 10^6] / [\text{Impedance } (\Omega) \times 1,000 \text{ (ms/s)}]$.¹⁸ Echocardiography was performed at least annually.

Statistical Analysis

Numerical data are expressed as median and range or as mean $\pm$ SD. The actuarial survival and freedom from reoperation for lead replacement was analyzed using the Kaplan-Meier method, and differences between groups were analyzed using log-rank statistics. Risk factors for lead failure were evaluated on univariate Cox regression hazard modeling; de-

mographic, anatomic, surgical, and clinical factors were considered. Factors with $P < 0.1$ on univariate analysis were entered as candidate factors into multivariate Cox regression, proportional hazards model. Confidence intervals (CI) at 95% are presented for the hazard ratios (HR). Comparisons among more than 3 groups were made using 1-way analysis of variance with a post-hoc comparison. Correlations between QRS duration and echocardiography were analyzed using linear regression analysis. The level of statistical significance was set at $P=0.05$; data were analyzed using the JMP® 9 (SAS Institute, Cary, NC, USA).

Results

Mortality

There were 4 early deaths and 6 late deaths. The reasons for the deaths were heart failure ($n=5$), respiratory infection ($n=3$), pulmonary embolism ($n=1$), and encephalopathy ($n=1$). Patient survival curves, according to cardiac structure, are shown in Figure 1. Deaths did not occur in patients without structural heart disease. Moreover, there were no deaths related to pacing system failure or pacing system infection.

Figure 3. Minimal energy threshold (MET) of 2 common ventricular leads at 1 month, 1 year, 3 years, and 5 years after ventricular lead implantation. The redo 4968 lead (4968R) was associated with significantly lower MET than the redo 5071 lead (5071R). 4968P, primary 4968 lead; 5071P, primary 5071 lead.

Table 3. Patients With Lead Replacement for Ventricular Dysfunction

Patient ID no.	Diagnosis	Age (years)		Location of ventricular lead		Assessment of pacing site	Concomitant procedure
		Previous PMI	Lead revision	Previous PMI	Lead revision		
1	TOF, postop AVB	3.4	17	LV base	LV apex		VVI → DDD
2	Congenital AVB	0.2	3.8	RV lateral	LV apex		
3	cTGA, VSD, congenital AVB	0.2	0.9	RV base	RV apex		Functional Repair
4	PA/VSD, postop AVB	11.5	12.1	RV lateral	LV apex	TEE	Conduit replacement, tricuspid annuloplasty
5	PA/VSD, postop AVB	11.9	15.0	RV lateral	LV apex	TEE	
6	SV, asplenia, postop AVB	12.4	13.1	RV base	RV apex		
7	AVSD, polysplenia, SND+acquired AVB	0.3	1.6	RV lateral	RV mid-anterior	Test pacing+TEE	
8	Congenital AVB	1.2	4.7	LV base	LV apex	Test pacing+TEE	

Patient ID no.	Outcome	Ventricular function		BNP (pg/ml)		QRS duration (ms)	
		Before	After	Before	After	Before	After
1	Improved	0.17 (LVFS)	0.38 (LVFS)	157	34.7	(–)	167
2	Improved	0.24 (LVFS)	0.41 (LVFS)	18.2	10.2	134	166
3	Unchanged, late death	43 (RVEF)	(–)	815	1,170	110	100
4	Improved	0.09 (LVFS)	0.41 (LVFS)	1,060	54.4	200	233
5	Improved	0.19 (LVFS)	0.24 (LVFS)	129	37.9	174	125
6	Early death	0.11 (SVFS)	(–)	891	(–)	146	(–)
7	Improved	Interventricular dyssynchrony	Dyssynchrony (–)	302	165	146	120
8	Improved	0.14 (LVFS)	0.48 (LVFS)	327	12.1	211	180

AVB, atrioventricular block; AVSD, atrioventricular septal defect; BNP, B-type natriuretic peptide; cTGA, congenitally corrected transposition of the great arteries; FS, fractional shortening; f-TCPC, fenestrated total cavopulmonary connection; LV, left ventricle; PA/VSD, pulmonary atresia with ventricular septal defect; RV, right ventricle; RVEF, right ventricular ejection fraction; SND, sinus node dysfunction; SV, single ventricle; TEE, transesophageal echocardiography. Other abbreviations as in Table 1.

Ventricular Lead Follow-up and Performance

During a median follow-up of 2.8 years (range, 0.2–10.5 years), 10 ventricular leads had to be replaced owing to lead failure. The freedom from ventricular lead failure was 96.3%, 86.8%, and 81.0% at 1, 3, and 5 years, respectively; predictors of ventricular lead failure are listed in **Table 2**. The independent predictors were age (HR, 0.879; 95% CI: 0.742–0.987; $P=0.026$), and peak MET within 6 months (HR, 1.036; 95% CI: 1.003–1.071; $P=0.035$). The MET peaks within 6 months, according to the 4 epicardial leads, are given in **Figure 2**. The 4968, steroid-eluting, bipolar, suture leads had significantly lower MET peaks than did the 5071, non-steroid-eluting, unipolar, screw leads (Medtronic; $P=0.02$). Furthermore, these 2 commonly used ventricular leads (4968, $n=30$; 5071, $n=20$) were subdivided into 4 groups (primary/redo), and MET was compared at 1 month, 1 year, 3 years, and 5 years after surgery (**Figure 3**). At each measured point, redo 4968 leads had significantly lower MET than did redo 5071 leads ($P=0.0009$ – 0.03). In addition, there were no significant differences between the primary 4968 leads and redo 4968 leads.

Pacemaker System Repositioning for Ventricular Dysfunction

During the study period, 8 patients underwent ventricular lead

replacement owing to pacing-induced ventricular dysfunction or to improve ventricular synchrony (**Table 3**). Two patients (nos. 4, 5) had previously undergone emergency lead implantations on the RV free wall via a subxiphoidal approach due to LV lead fracture. After operation, LV dysfunction and dilatation gradually developed. Another patient (no. 2) had undergone RV apical pacing at another hospital. For assessment of the appropriate pacing site, 2 patients underwent preoperative cardiac catheterization and test pacing using a pacing catheter, and 4 patients underwent intraoperative, transesophageal echocardiography. Postoperative transthoracic echocardiography showed improved systemic ventricular function in 6 patients, and these improvements were maintained, thereafter. Pacing system repositioning, however, was not effective in 2 patients. One of these patients (no. 6) had heterotaxy syndrome and severe, preoperative heart failure requiring postoperative extracorporeal membrane oxygenation support for hemodynamic instability; that patient eventually died due to ventricular dysfunction and multiple organ failure. Another patient (no. 3), with congenitally corrected transposition of the great arteries, underwent functional biventricular repair and ventricular lead replacement on the RV apex. Although the postoperative course was uneventful, no improvement in systemic RV function was confirmed on postoperative echocardiography; he

died 6 months later from acute enteritis.

Follow-up

At a median follow-up of 59 months (range, 6–134 months), the ventricular pacing site was the LV in 28 patients, the RV in 9 (transvenous, $n=5$), and an SV in 8 patients. The reason for epicardial RV pacing in 4 patients was previous multiple surgeries in 2, twitching owing to LV pacing in 1, and before 2005 in 1. The QRS duration was 164 ± 30 ms during LV pacing, 180 ± 31 ms during RV pacing, and 150 ± 31 ms during SV pacing, respectively ($P=0.19$). The systemic ventricular fractional shortening was 0.34 ± 0.09 during LV pacing, 0.30 ± 0.08 during RV pacing, and 0.24 ± 0.06 during SV pacing, respectively. In the patients with biventricular heart, LV fractional shortening was not correlated with QRS duration ($R^2=0.019$, $P=0.47$). None of the patients with LV pacing had severe ventricular dysfunction or dilatation, whereas 1 patient with RV pacing had severe ventricular dysfunction.

Discussion

Although controversies about the indications for transvenous or epicardial pacing systems in the pediatric age group still exist,^{1–3,5–8} our policy has been to maintain epicardial pacing until the patient reaches adulthood. Although reoperations are inevitable problems associated with pediatric pacemaker therapy, previous reports have focused on the results of primary procedures.^{2,3,7–9} Reports describing the strategies for reoperation, including surgical approach and lead selection are limited.¹⁰

Pacing-Induced Heart Failure

The RV apex has been the most prevalent site for endocardial pacing for decades,¹ and the RV free wall has been the preferred site for epicardial pacing at many pediatric centers because of its accessibility.^{2,3,11} RV pacing-induced ventricular remodeling and heart failure, however, have gradually been recognized over the last decade.^{1–3,10–17} Gebauer and Tomek evaluated the LV function of 82 pediatric patients with complete AVB who had been 100% RV paced.¹¹ The incidence of LV dilatation or dysfunction was 13.4% (11/84), and epicardial RV free wall pacing was the only independent risk factor for the development of late LV dilatation and dysfunction. Animal and human studies have also demonstrated dyssynchronous LV contraction induced by RV pacing.^{12–14} Janoušek et al reported the results of a multicenter study involving speckle tracking analysis of precise ventricular functions, according to the ventricular pacing site, in children with congenital heart block who underwent permanent pacemaker implantation.¹² In that study, LV synchrony, pump function, and contraction efficiency were preserved in children paced at the LV apex/LV lateral wall, whereas they were significantly depressed in children paced at the RV outflow tract/RV lateral wall. According to these reports, there is little doubt that the left LV apex and LV lateral wall are the ideal locations for pediatric patients who need lifelong pacing. In the current study, QRS duration was not significantly different according to ventricular pacing site. In addition, it was not correlated with LV function. These findings are consistent with other studies.^{12,16,17} Based on these results, QRS duration could not be used as a tool for evaluating optimal pacing site in patients with single-site pacing.

Cardiac resynchronization therapy (CRT) was developed and advanced as a treatment for patients with advanced heart failure associated with intraventricular conduction disturbance.¹⁹

In Japan, CRT was included in the National Health Insurance price list in 2004, and the latest guideline of the Japanese Circulation Society for CRT in adult patients was published in 2013.²⁰ Recently, the efficacy of CRT in pediatric and congenital heart disease patients has also been reported.^{21–24} According to these reports, a significant proportion of patients undergoing CRT had RV pacing-induced ventricular failure. The patients with RV pacing-induced LV failure were considered to be good candidates for CRT, these patients are potentially good candidates for ventricular lead revision to the LV apex.²⁵ In addition, maintaining life-long CRT for pediatric patients seems to be more challenging than single-site LV pacing. According to the multicenter study on pediatric CRT, reported by Janoušek et al, 7 of 109 patients (6.4%) had to discontinue CRT within a short follow-up period (median, 7.5 months).²¹

In contrast to patients with systemic LV pacing, determination of the optimal ventricular pacing site for patients with SV or systemic RV pacing was challenging. In the present study, only 1 of the 3 patients had clinical improvement after ventricular lead repositioning. Although the results of multicenter studies for these patient groups were also inconsistent,^{21,22} CRT has several advantages that would facilitate improvement of interventricular dyssynchrony, such as multisite pacing and programmability of the interventricular interval. Most children's hospitals in Japan, including Kobe Children's Hospital, however, could not use CRT devices owing to the strict criteria set by the Japanese Ministry of Health, Labor and Welfare for the national insurance scheme.²⁴ In either case, preoperative ventricular stimulation, using a pacing catheter and modern echocardiographic analysis, may assist in making these decisions, including the indication for CRT. In addition, these procedures should be considered before irreversible ventricular deterioration occurs.

Lead Selection for Reoperation

In this study, we focused on the analysis of ventricular lead function because it was directly related to indication for reoperation. Prior studies have also reported superior pacing properties of steroid-eluting leads over non-steroid-eluting leads.^{2,5–7} Unique to the present study, however, these differences were more apparent in the reoperation patients. During the study period, 3 of 6 patients with reoperation involving 5071 leads had early increases in the pacing threshold ($MET > 5 \mu J$, within 6 months), whereas none of the 14 patients with reoperation involving 4968 leads had similar increases. These experiences indicate that the current first choice for ventricular leads in patients requiring reoperation is the 4968 lead. If an acceptable pacing threshold cannot be achieved using this lead, the next option is the non-steroid-eluting bipolar screw-in lead (51121; Greatbath Medical, Fort Wayne, IN, USA). At the time of writing, the screw-type, bipolar, steroid-eluting, epicardial pacing lead (Myodex 1084T; St. Jude Medical, St. Paul, MN, USA) has just become available, and may contribute to the advancement of pediatric pacemaker therapy.

Study Limitations

This study has several limitations. In addition to its retrospective nature, it has the usual potential for bias due to the small sample size from a single center. Owing to the very few cases of transvenous pacing (5 patients), we were unable to compare the transvenous pacing group to the epicardial pacing group. Furthermore, the 2 commonly used ventricular leads were bipolar steroid-eluting leads and unipolar non-steroid-eluting leads. We could not determine whether the superiority of the

4968 lead was due to its steroid elution or its bipolar configuration. The lack of comparison between CRT and LV pacing was another major limitation of this study. In addition, ventricular function was assessed only using conventional echocardiographic parameters. Recently, more precise evaluations of ventricular contraction and mechanical synchrony have become possible using speckle tracking echocardiography.

Conclusions

The outcome of an LV apex-prioritized pacing strategy, in pediatric patients, is excellent and preserves ventricular function. Bipolar, steroid-eluting, epicardial pacing leads had good pacing properties even in reoperation patients. In children with systemic LV and pacing-induced ventricular dysfunction, conversion to single-site LV apex pacing seems to be an attractive alternative to an upgrade to CRT. This study was not supported by any grants or other funding.

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