Outcome of patients with functional single ventricular heart after pacemaker implantation: What makes it poor, and what can we do?

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Outcome of patients with functional single ventricular heart after pacemaker implantation: What makes it poor, and what can we do?

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BACKGROUND Pacemaker implantation in patients with single ventricle is associated with poor outcomes.

OBJECTIVE The purpose of this study was to determine the reasons for the poor outcomes of pacemaker implantation.

METHODS We performed a retrospective chart review of patients with single ventricle who had undergone permanent pacemaker implantation. Patients were categorized into 3 groups based on the site of pacing and the proportion of ventricular pacing (VP) as follows: (1) atrial pacing group with atrial pacing only (n = 11); (2) low VP group with low daily VP proportion (<50%; n = 12); and (3) high VP group with high daily VP proportion (≥50%; n = 15). Pacing leads were placed at the epicardium in all patients.

RESULTS No patients in the atrial pacing or low VP groups died, whereas the survival rate in the high VP group was 58.9% and 39.3% at 10 and 20 years, respectively, after pacemaker implantation. Among the post-Fontan patients, plasma brain natriuretic peptide (BNP) levels significantly increased with the proportion of VP: 11.7, 20.3, and 28.4 pg/mL in the atrial pacing, low VP, and high VP groups, respectively ($P = 0.04$). In the high VP group, the plasma BNP level was significantly lower in patients with an apical pacing lead than in those with a nonapical pacing lead (27.0 pg/mL vs 82.8 pg/mL, respectively; $P = .03$).

CONCLUSION A higher proportion of VP was associated with poor outcome and higher plasma BNP levels, probably due to ventricular dyssynchrony. In epicardial ventricular pacing, apical pacing is better to avoid the increase in ventricular stress and plasma BNP level.

KEYWORDS Apical pacing; Epicardial lead; Fontan procedure; Functional single ventricle; Pacemaker implantation

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Introduction

Staged Fontan procedure has been performed widely in patients with severe congenital heart diseases for whom surgical biventricular repair is unsuitable.[1,2] The aim of treatment of these patients is completion of the Fontan procedure during early childhood, but complications and death occur frequently both before and after the Fontan procedure.[3–7] Bradyarrhythmia is a major complication and can result from congenital abnormalities of the conduction system.[8,9] It is often complicated by polysplenia (usually left isomerism) and an L-looped ventricle or by surgical injury.[10–12] Pacemaker implantation has been shown to be related to poor outcomes in patients with functional single ventricle (SV).[4,13] Previous studies have investigated patients with SV who have undergone pacemaker implantation; however, the detailed outcomes and contributing factors were not completely investigated.[8–10,14,15] We hypothesized that lead position and proportion of pacing are factors related to poor outcome.

The aim of this study was to investigate survival and ventricular function after pacemaker implantation in patients with SV physiology, before and after the Fontan procedure, and to determine the effects of different lead positions and proportion of pacing on outcome in patients with functional single ventricular heart and pacemaker implantation.

Methods

We conducted a retrospective chart review of all patients with functional SV who underwent permanent pacemaker implantation at Fukuoka Children's Hospital (FCH) and were

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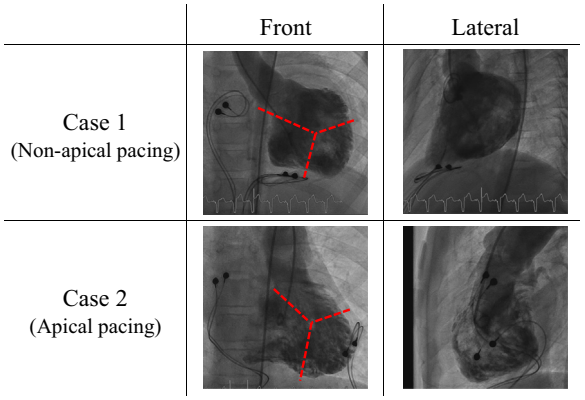

Figure 1 Definition of lead position. The ventricular image is divided into 3 equal portions: inflow, apex, and outflow. Case 1 shows nonapical pacing, in which the lead is positioned on the inferior wall of the inflow. Case 2 shows apical pacing.

followed up by FCH and Kyushu University Hospital (KUH). Both institutions are tertiary care centers. The majority of the local patients with SV were managed at FCH during childhood and then transferred to the adult congenital heart disease clinic at KUH after adolescence. Data were collected using a research electronic data capture system (REDCap), which was an electronic data capture tool hosted at Kyushu University. The study protocol was approved by the institutional review boards at both hospitals.

Patients

All patients who underwent pacemaker implantation between 1980 and 2016 at FCH were enrolled in the study. Patients who have previously undergone atrioventricular valve replacement, during which complete atrioventricular block frequently occurs, were excluded from the study because the outcome would have been severely affected by the valve replacement itself. Also excluded from the analysis were patients in whom the pacemaker had become unnecessary and had been removed, those in whom the pacemaker was indicated for cardiac resynchronization therapy, and those with unrecorded details.

Because we intended to compare the outcomes of patients with and those without ventricular pacing (VP), the simple categorization of patients based on the presence of a ventricular lead was inadequate because some of the ventricular leads may have been inserted only for occasional backup use, and in such cases the daily proportion of VP is small. Therefore, we categorized patients according to the presence of a ventricular lead and the proportion of VP. The atrial pacing group comprised patients who had only an atrial lead without a ventricular lead. The low VP group comprised patients who had a ventricular lead with a daily VP proportion $<50\%$. The high VP group comprised patients who had a ventricular lead with a daily VP proportion $\geq 50\%$. The proportion of VP was estimated by routine pacemaker checkup

Table 1 Patient characteristics

	Atrial pacing group (no VP)	Low VP group (VP <50%)	High VP group (VP ≥50%)	*P* value
No.	11	12	15	
Female	6 (54.5)	5 (41.7)	7 (46.7)	.92
Birth weight (g)	2726 (2413–2913)	2957 (2458–3254)	3006 (2745–3283)	.11
Diagnosis				
TA	2 (18.2)	3 (25.0)	2 (13.3)	
PAIVS	0	1 (8.3)	0	
HLHS	4 (36.4)	2 (16.7)	2 (13.3)	.71
Other LV	1 (9.1)	2 (16.7)	5 (33.3)	
Other RV	4 (36.4)	4 (33.3)	6 (66.6)	
Heterotaxy				
Asplenia	0	1 (8.3)	1 (6.6)	1
Polysplenia	6 (54.5)	1 (8.3)	1 (6.6)	.008
Primary indication for PM				
SSS/AV dissociation	11 (100)	3 (25.0)	3 (20.0)	
Complete AV block	0	1 (8.3)	4 (26.7)	<.001
Other AV block	0	8 (66.6)	8 (53.3)	
PM type				
AAI	11 (100)	0	0	
VVI	0	5 (41.7)	5 (33.3)	<.001
DDD	0	7 (58.3)	10 (66.6)	
Age at pacemaker implantation (y)	3.0 (1.8–6.2)	7.2 (3.5–12.5)	2.2 (0.7–5.9)	.06
Timing of operation				
At/after palliation	0	0	3 (20.0)	
At/after Glenn	1 (9.1)	1 (8.3)	6 (40.0)	.01
At/after Fontan	10 (90.1)	11 (91.7)	6 (40.0)	
Concomitant procedure	0	0	1 (6.6)	1
Patients born in the first half series	3 (27.3)	7 (58.3)	9 (60.0)	.22

Data are given as n, n (%), or median (interquartile range, first to third).

AV = atrioventricular; HLHS = hypoplastic left heart syndrome; LV = left ventricle; PAIVS = pulmonary atresia with intact ventricular septum; PM = pacemaker; RV = right ventricle; SSS = sick sinus syndrome; TA = tricuspid atresia; VP = ventricular pacing.

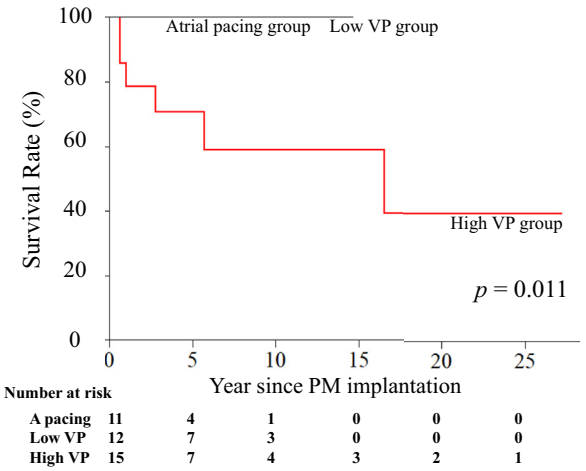

Figure 2 Kaplan–Meier survival curve according to ventricular pacing (VP). The survival rate of the high VP group is significantly worse than that of the other groups. PM = pacemaker.

or Holter electrocardiograms. The high VP group was further divided based on the location of the ventricular lead into apical and nonapical pacing subgroups. The site of the ventricular lead was determined based on ventriculogram by equally dividing the ventricle into the 3 portions: inflow, apex, and outflow (Figure 1).

For assessment of ventricular function by ejection fraction, atrioventricular valvular regurgitation, and plasma brain natriuretic peptide (BNP) levels among the 3 groups, we extracted and compared only post-Fontan patients to unify the background hemodynamics. Ejection fraction and atrioventricular valvular regurgitation were analyzed based on the last ventriculogram, and plasma BNP levels were obtained from the last outpatient clinic visit.

Statistical analysis

Continuous data are expressed as median (interquartile range, first to third) and categorical data as frequency (%). Kaplan–Meier and log-rank methods were used to compare cumulative survival rates. The Mann–Whitney *U* test and Fisher exact probability test were used to compare independent variables. $P < .05$ was considered significant. R version 3.3.1 software (www.r-project.org) was used for statistical analysis.

Results

A total of 38 patients were included in the study population after 12 patients were excluded because of previous atrioventricular valvular replacement in 6, eventual removal of the pacemaker in 4, cardiac resynchronization therapy as the indication for pacemaker implantation in 1, and the absence of detailed records in 1. All leads were placed by an epicardial procedure. Table 1 lists the patient characteristics of the atrial pacing (n = 11), low VP (n = 12), and high VP groups (n = 15). Of note, there was a substantial gap in the proportion of VP between the low VP and high VP groups. The highest proportion in the low VP group was 25%, and the lowest proportion in the high VP group was 52%. The average follow-up period was 6.7 ± 6.1 years. There were no significant differences with regard to sex, birth weight, and anatomic diagnosis among the 3 groups. With regard to heterotaxy, the prevalence of polysplenia was significantly higher in the atrial pacing group than in the other groups; this reflected the tendency for patients to develop sick sinus syndrome, which requires an atrial pacing pacemaker. In addition, the timing of pacemaker implantation was later in the atrial pacing group than in the other groups. Complete atrioventricular block in 1 patient in the low VP group and 4 patients in the high VP group was the result of surgery or catheter procedures.

The outcome of pacemaker implantation differed significantly among the 3 groups (Figure 2). All patients in the atrial pacing and low VP groups survived at the time of data collection, whereas 6 deaths occurred in the high VP group (2 due to ventricular dysfunction, 1 cerebral hemorrhagic infarction, 1 pacing failure, 1 liver cirrhosis, 1 encephalopathy). The survival rate of the high VP group was 58.9% and 39.3% at 10 and 20 years, respectively, after pacemaker implantation.

The patients were divided equally into 2 groups as the first half and second half series in order to determine the era effect (n = 19 in each group). Five deaths and 1 death occurred in the 2 groups, respectively, but the difference was not statistically significant (log-rank test, $P = .16$).

In the analysis of ventricular function, no differences were seen among the groups in terms of ejection fraction and the prevalence of moderate-to-severe atrioventricular valvular regurgitation, whereas plasma BNP levels were significantly increased according to the proportion of VP (Table 2). The apical pacing and nonapical pacing subgroups of the high VP group had similar trends in outcome in terms of survival (Figure 3); however, plasma BNP levels differed significantly among post-Fontan procedure patients (Table 3).

Table 2 Ventricular function and plasma BNP level at last follow-up among post-Fontan patients

	Atrial pacing group (no VP)	Low VP group (VP <50%)	High VP group (VP ≥50%)	*P* value
No.	11	12	11	
Ejection fraction (%)	58.4 (55.4–65.2)	59.0 (65.3–64.6)	55.9 (51.4–58.4)	.41
AVVR ≥ moderate (%)	0	0	1 (9.1)	.65
BNP (pg/mL)	11.7 (7.4–22.6)	20.3 (10.5–33.1)	28.4 (26.2–43.1)	.04

Data are given as n, n (%), or median (interquartile range, first to third).
AVVR = atrioventricular regurgitation; BNP = brain natriuretic peptide; VP = ventricular pacing.

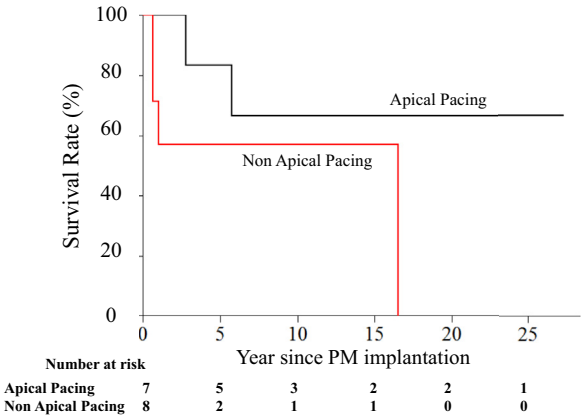

Figure 3 Kaplan–Meier survival curve according to ventricular lead position in the high ventricular pacing (VP) group. The apical and nonapical pacing subgroups of the high VP group had similar trends of outcome. PM = pacemaker.

Discussion

In this single-institution study, we analyzed survival and ventricular function after pacemaker implantation in patients with SV physiology. Our results showed that the high proportion of VP is associated with poor survival rate, and an epicardial ventricular lead position in the apex may be better in such patients. To our knowledge, this is the first report to compare the outcome of SV patients with pacemaker implantation according to the proportion of pacing and pacemaker lead position. The largest registry of Fontan patients showed that pacemaker implantation was one of the independent factors related to late adverse events.[4] One study reported poor outcome in patients who required pacemaker implantation before a Fontan procedure,[13] but another report showed a contrary result.[9]

Although pacemakers in such patients are associated with adverse outcomes, the mechanisms remain unclear. Bradyarrhythmia itself likely is a high-risk factor for mortality; in fact, 1 patient in this study died of pacemaker lead failure. However, this death accounts for only a small proportion of the mortalities, and the cause of death of the other 5 patients in this study had no direct relationship with the bradyarrhythmia itself. As shown in Figure 2, mortality was observed only in patients with a high proportion of VP, and plasma BNP levels in this group were higher than in the other 2 groups. In general, a high proportion of VP is a known risk factor for hospitalization due to heart failure in adult patients with bradyarrhythmia.[16,17] Therefore, a plausible explanation would be that the high proportion of VP in our cohort caused ventricular dyssynchrony and poor long-term outcome. This was supported by the observation that 2 patients died of ventricular dysfunction.

Another cause of death was cerebral hemorrhagic infarction, which we believe can be attributed to pacemaker implantation, as a previous study on SV physiology reported a relatively frequent occurrence of thrombotic events in patients with a pacemaker.[8] However, the impact of pacemaker implantation on death in the other 2 patients (liver cirrhosis and encephalopathy) is difficult to interpret. Ejection fraction as determined by ventriculogram was preserved in these 2 cases. Although we cannot deny that the pacemaker may have influenced, to some degree, the course and therapeutic process of those incidental complications, the exact relationship between pacemaker and mortality cannot be ascertained.

VP is widely recognized to cause ventricular dyssynchrony, based on the location of the ventricular lead. In the general population of adult patients with bradyarrhythmia, the ventricular septum is considered to be the optimal endocardial lead position to prevent ventricular dyssynchrony[18,19] because the pattern of ventricular excitation resembles the physiological one. Comparable studies in pediatric patients with congenital complete atrioventricular block have been performed.[20,21] However, we cannot consider endocardial and epicardial pacing in the same manner. For the epicardial pacing performed in this study population, apical pacing was reported to be useful in preventing ventricular dyssynchrony, and left ventricular pacing was found to be better than right ventricular pacing.[22–25] Because differentiation of the ventricle from the right and left sides is difficult because of the various functional SV morphologies in our cohort, we divided the patients into 2 groups (apical and nonapical pacing) for analysis. Our results suggest that the better pacing site might be the ventricular apex. This is an important finding regarding the optimal VP site for patients with SV.

Although speckle tracking with echocardiography is frequently used in the evaluation of ventricular dyssynchrony,[24,25] plasma BNP level is also reported to be a useful index of dyssynchrony.[18,26] Because this study was based on retrospective chart review, a detailed echocardiographic evaluation of dyssynchrony was not feasible. Furthermore, measurements of ventricular volume in this study were based on ventriculogram images, for

Table 3 Ventricular function and plasma BNP level at last follow-up among post-Fontan patients in the high VP group

	Apical pacing	Nonapical pacing	*P* value
No.	7	4	
Ejection fraction (%)	54.7 (51.4–58.4)	55.9 (52.9–60.3)	.9
AVVR ≥ moderate (%)	0	1 (25)	.4
QRS width (ms)	136 (128–146)	142 (139–149)	.22
BNP (pg/mL)	27 (23.7–28.4)	82.8 (60.4–98.9)	.03

Data are given as n, n (%), or median (interquartile range, first to third).
AVVR = atrioventricular regurgitation; BNP= brain natriuretic peptide; VP = ventricular pacing.

which accuracy is generally limited; this might have resulted in inaccurate measurements of ejection fraction. Plasma BNP level was shown to increase as the proportion of VP increased and was higher in patients with nonapical than apical pacing. This trend probably was related to ventricular dyssynchrony caused by VP. We believe the reason for the significant difference observed only in plasma BNP level can be attributed to the sensitive nature of BNP level as an index of ventricular dyssynchrony. Further study using speckle tracking with echocardiography would be needed to clarify the reason for the poor outcome of pacemaker implantation and to determine the optimal epicardial VP site.

Study limitations

First, it was difficult to statistically analyze the outcome in the subgroup analysis because of the small sample size. Second, because ventricular morphology widely varies among patients with functional SV, measurements of ventricular volume by ventriculogram might be inaccurate; therefore, the statistical appropriateness of ejection fraction could be limited. Third, although the normal range of plasma BNP level and ejection fraction may differ among the primary diagnoses, the small population number precluded us from accounting for these differences. Fourth, due to the significant difference in background, including time of pacemaker implantation, the difference in outcomes might have been skewed according to pacing location and proportion. Lastly, we could not determine the details of cause of death because of the retrospective nature of this study based on chart review. Therefore, the causal relationship between pacemaker implantation and death was not clear in some cases.

Conclusion

The survival rate among patients with SV who have undergone pacemaker implantation was lower in patients with a higher proportion of VP. Plasma BNP levels were higher in patients with a higher proportion of VP, implying a relationship with ventricular dyssynchrony. The ventricular apex might be recommended as an epicardial pacing site for these patients to prevent increased ventricular stress and plasma BNP levels.

References

1. Pridjian AK, Mendelsohn AM, Lupinetti FM, et al. Usefulness of the bidirectional Glenn procedure as staged reconstruction for the functional single ventricle. Am J Cardiol 1993;71:959–962.
2. Masuda M, Kado H, Shiokawa Y, et al. Clinical results of the staged Fontan procedure in high-risk patients. Ann Thorac Surg 1998;65:1721–1725.
3. Pundi KN, Johnson JN, Dearani JA, et al. 40-Year follow-up after the Fontan operation long-term outcomes of 1,052 patients. J Am Coll Cardiol 2015; 66:1700–1710.
4. D'udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 2014; 130:S32–S38.
5. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol 2014;64:54–62.
6. Idorn L, Olsen M, Jensen AS, et al. Univentricular hearts in Denmark 1977 to 2009: incidence and survival. Int J Cardiol 2013;167:1311–1316.
7. Fixler DE, Nembhard WN, Salemi JL, Ethen MK, Canfield MA. Mortality in first 5 years in infants with functional single ventricle born in Texas, 1996 to 2003. Circulation 2010;121:644–650.
8. Williams RV, Travison T, Kaltman JR, et al. Comparison of Fontan survivors with and without pacemakers: a report from the Pediatric Heart Network Fontan Cross-Sectional Study. Congenit Heart Dis 2013;8:32–39.
9. Egbe AC, Huntley GD, Connolly HM, et al. Outcomes of cardiac pacing in adult patients after a Fontan operation. Am Heart J 2017;194:92–98.
10. Niu MC, Dickerson HA, Moore JA, et al. Heterotaxy syndrome and associated arrhythmias in pediatric patients. Heart Rhythm 2018;15:548–554.
11. Loomba RS, Willes RJ, Kovach JR, Anderson RH. Chronic arrhythmias in the setting of heterotaxy: differences between right and left isomerism. Congenit Heart Dis 2016;11:7–18.
12. Simmons MA, Rollinson N, Fishberger S, Qin L, Fahey J, Elder RW. Modern incidence of complete heart block in patients with L-looped ventricles: does univentricular status matter? Congenit Heart Dis 2015;10:E237–E242.
13. Mah DY, Cheng H, Alexander ME, et al. Heart block following stage 1 palliation of hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2016;152:189–194.
14. Stephenson EA, Lu M, Berul CI, et al. Arrhythmias in a contemporary Fontan cohort prevalence and clinical associations in a multicenter cross-sectional study. J Am Coll Cardiol 2010;56:890–896.
15. Bulic A, Zimmerman FJ, Ceresnak SR, et al. Ventricular pacing in single ventricles—a bad combination. Heart Rhythm 2017;14:853–857.
16. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–2937.
17. Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006;113:2082–2088.
18. Dehnavi AM, Fakhrpour A, Tavakoli MB, Nikoo MH. Investigation of the BNP level changes in blood stream in different modes and lead locations after pacemaker implementation. J Med Signals Sens 2012;2:38–41.
19. Cano O, Osca J, Sancho-Tello MJ, et al. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. Am J Cardiol 2010; 105:1426–1432.
20. Silvetti MS, Ammirati A, Palmieri R, et al. What endocardial right ventricular pacing site shows better contractility and synchrony in children and adolescents? Pacing Clin Electrophysiol 2017;40:995–1003.
21. Karpawich PP, Singh H, Zelin K. Optimizing paced ventricular function in patients with and without repaired congenital heart disease by contractility-guided lead implant. Pacing Clin Electrophysiol 2015;38:54–62.
22. Matsuhisa H, Oshima Y, Maruo A, et al. Pacing therapy in children. Circ J 2014; 78:2972–2978.
23. Raichlen JS, Campbell FW, Edie RN, Josephson ME, Harken AH. The effect of the site of placement of temporary epicardial pacemakers on ventricular function in patients undergoing cardiac surgery. Circulation 1984; 70:I118–I1123.
24. Tomaske M, Breithardt OA, Bauersfeld U. Preserved cardiac synchrony and function with single-site left ventricular epicardial pacing during mid-term follow-up in paediatric patients. Europace 2009;11:1168–1176.
25. Janoušek J, Van Geldorp IE, Krupičková S, et al. Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study. Circulation 2013;127:613–623.
26. Guimaraes Abreu CD, Pereira Nunes M do C, Barbosa MM, Costa Rocha MO, Pinho Ribeiro AL. Ventricular dyssynchrony and increased BNP levels in right ventricular apical pacing. Arq Bras Cardiol 2011;97:156–162.