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Original Article

Clinical outcomes and left ventricular systolic function changes after right ventricular pacing in patients with complete atrioventricular block

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Abstract: Background: Permanent pacemakers are routinely used to treat patients with complete atrioventricular block. However, as patient characteristics and treatment concepts have changed, little is known about clinical outcome and echocardiographic changes in a real-world cohort of patients with complete atrioventricular block after right ventricular pacing. Methods: Patients with first-time permanent pacemaker implantation due to complete atrioventricular block were enrolled between January 1, 2011, and June 30, 2020, with all-cause death and hospitalization for heart failure as study endpoints, and changes in left ventricular systolic function during follow-up were analyzed. Results: A total of 460 patients were enrolled, with an average age of 69.9±12.4 years. The mean left ventricular ejection fraction (LVEF) was 57.71±12.63%. Fifty-five patients (12.0%) had an LVEF below 50%. The median follow-up time was 50.7 (26.2, 80.5) months, and the event-free survival rate was 91.3% for all-cause death and 85.4% for heart failure hospitalization. During follow-up, 90.1% of patients with preoperative LVEF ≥ 50% had a normal left ventricular function. Multivariate analysis showed that each percentage increment in LVEF was associated with a 3% (95% CI, 1-5%) reduction in heart failure hospitalization, whereas RV pacing percentage was a predictor of heart failure hospitalization (HR, 1.053; 95% CI 1.012-1.096). Conclusion: Permanent pacemaker implantation provided a favorable clinical prognosis in a population where most patients retained left ventricular function with complete atrioventricular block.

Keywords: Atrioventricular block, pacemaker, prognosis, left ventricular function

Introduction

Permanent pacemaker implantation significantly improves survival and quality of life in patients with complete atrioventricular block, and has been a routine treatment for such patients since the advent of the pacemaker [1]. Studies have shown that the prognosis of patients after permanent pacemaker implantation mainly depends on underlying diseases and complications, and the survival rate of patients with cardiovascular diseases is significantly lower than that of the general population [2-4]. Patients undergoing pacemaker implantation in clinical practice are often older and have more coexisting diseases as they age. On the other hand, the treatment concept for cardiovascular disease has been constantly updated in recent years. These factors may affect the prognosis of pacemakers. An analysis of data from patients with pacemakers implanted between 1975 and 2004 found that having pacemakers implanted later was an independent predictor of survival [5].

Recent studies have shown that patients with conventional pacemakers have good outcomes in terms of heart failure hospitalization [6, 7] and mortality [8]. However, the patients rec ruited in these studies were preselected, and few studies have evaluated the echocardiographic course of left ventricular function. Therefore, the present study aimed to retrospectively analyze clinical outcomes and echocardiographic changes in a real-world cohort of patients with complete atrioventricular block who underwent permanent pacemaker implantation.

Patients and methods

Patients

This study retrospectively enrolled patients who underwent single- or dual-chamber pacemaker implantation for complete atrioventricular block for the first time, as well as had clinical and echocardiographic follow-up at the Department of Cardiology, Foshan First People's Hospital, Guangdong Province, between January 1, 2011, and June 30, 2020. Patients with the following conditions were excluded: (1) age < 18 years; (2) drug-induced or reversible atrioventricular block; (3) malignant tumor or disturbance of consciousness; and (4) implantation of cardiac resynchronization therapy device (CRT). All the patients signed a consent statement before the procedure. This study was approved by the institutional review board of our institution.

Device implantation procedure

A pacemaker was implanted under fluoroscopic guidance in all patients. The right ventricular (RV) lead was placed at the upper or middle septal segment, or at the RV apex. Physicians determined the location of the RV pacing lead and the type of pacing device for each patient.

Routine pacemaker follow-up was recommended for all patients at 1, 3, 6 and 12 months postoperatively, and annually afterwards. Follow-up was performed by the attending physician of the cardiology department and the pacemaker engineer.

Echocardiographic follow-up

All the patients underwent transthoracic echocardiography before the procedure. During follow-up, the timing of the echocardiographic examination was determined by the physician according to the patient's condition and current practice guidelines. If multiple echocardiographic examinations were performed during the follow-up period, the most recent one was recorded. Echocardiographic measurements included left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV).

Clinical endpoints

The study's endpoints included all-cause death and hospitalization for heart failure. Endpoints were ascertained by reviewing electronic medical records or telephonic visits. Follow-up was calculated from the date of the procedure to the date of the endpoint event or the end of follow-up (August 1, 2021).

Statistical analysis

Statistical analysis was performed using SPSS version 24.0. Continuous variables following a normal distribution are presented as mean ± standard deviation, and those not in accordance with a normal distribution are presented as medians and quartiles. Categorical variables are expressed as proportions. The unpaired *t*-test was used to compare continuous variables. A paired *t*-test was used to compare preoperative and follow-up echocardiographic indicators. To reveal predictors of the outcomes, possible variables (age, sex, cerebrovascular disease, hypertension, diabetes, coronary artery disease, atrial fibrillation, heart failure, LVEF, pacing device, RV pacing lead site, and RV pacing percentage) were included in the Cox regression model. The Kaplan-Meier method was used for the survival curve. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics

A total of 460 patients (222 males, 48.3%) were enrolled, with an average age of 69.9± 12.4 years. The mean LVEF was 57.71±12.63%. The baseline characteristics and information regarding the cardiac pacing device are presented in **Table 1**.

Follow-up results of echocardiography

All the patients underwent transthoracic echocardiography after a median follow-up of 2.25 (0.86, 4.62) years. The changes in echocardiographic indicators are shown in **Table 2**, and there were no statistically significant differences in any of the indicators ($P > 0.05$). Patients with less than one year of follow-up and those with more than one year of follow-up were analyzed separately to illustrate if fol-

Table 1. Baseline characteristics and implanted pacing device

Variables	All patients (n=460)
Age, years	69.9±12.4
Male, n (%)	222 (48.3%)
Hypertension, n (%)	228 (49.6%)
Diabetes, n (%)	97 (21.1%)
Coronary artery disease, n (%)	43 (9.3%)
Atrial fibrillation, n (%)	35 (7.6%)
Cerebrovascular disease, n (%)	21 (4.6%)
Heart failure, n (%)	50 (10.9%)
LVEF, %	57.71±12.63
LVEF < 50%, n (%)	55 (12.0%)
Cardiac pacing device, n (%)	
Dual-chamber pacemaker, n (%)	403 (87.6%)
Single-chamber pacemaker, n (%)	57 (12.4%)
RV pacing lead site, n (%)	
RV apex, n (%)	179 (38.9%)
RV septum, n (%)	281 (61.1%)
RV pacing percentage at 6-month follow up	89.49±11.25

Note: LVEF, Left Ventricular Ejection Fraction; RV, Right Ventricular.

low-up duration had an effect on echocardiographic parameters. There was no statistically significant difference in any of the indicators in either group (**Table 3**).

At follow-up, among the patients with preoperative LVEF ≥ 50%, 365 (90.1%) maintained normal LVEF, 30 (7.4%) had mildly reduced LVEF between 40-49%, and 10 (2.5%) had LVEF < 40%. Among patients with preoperative LVEF of 40-49%, nine (31.0%) showed an improved LVEF to over 50%, nine (31.0%) remained unchanged with an LVEF between 40-49%, and 11 (37.9%) decreased LVEF to less than 40%. Among patients with preoperative LVEF < 40%, six (23.1%) had a normal LVEF > 50%, two (7.7%) had an improved LVEF between 40-49%, and 18 (69.2%) still had an LVEF < 40% (**Figure 1**).

In patients with an RV pacing lead in the apex, LVEF was 57.28±13.45 before the procedure and 56.96±14.80 at follow-up (*P*=0.81). In patients with an RV pacing lead in the septum, LVEF was 58.94±10.64 before the procedure and 57.88±11.32 at follow-up (*P*=0.42). There were no significant differences in LVEF changes between patients with different RV pacing lead sites (*P*=0.72) (**Figure 2**).

Follow-up results of clinical events

Patients were followed up for a median of 50.7 (26.2, 80.5) months. During the study period, 40 all-cause deaths and 67 hospitalizations for heart failure were recorded. The survival rates without all-cause death and heart failure hospitalization were 91.3% and 85.4%, respectively (**Figure 3**).

Predictors of outcomes

Table 4 summarizes the results of the multivariate regression analysis. Multivariate analysis revealed that male sex and age were the independent risk factors for all-cause death. Each percentage increment in LVEF was associated with a 3% (95% CI, 1-5%) reduction in heart failure hospitalization. The elevation of RV pacing percentage was associated with an increased risk of hospitalization for heart failure (HR, 1.053; 95% CI 1.012-1.096).

However, the multivariate analysis failed to identify the RV pacing lead site as a predictor of all-cause death and heart failure hospitalization.

Discussion

In a previous study, patients undergoing pacemaker implantation between 2003 and 2007 had 1-, 3-, 5-, and 7-year survival rates of 93%, 81%, 69%, and 61%, respectively [2]. Another study showed that patients with pacemaker implantation for atrioventricular block from 2000 to 2013 had an average follow-up of 46.5±43.2 months, and the annual mortality rate was 3.7% [9]. The all-cause death-free survival rate reported in this study was 91.3%, which was higher than that reported in the above studies, and it was speculated to be related to the different study subjects. Compared with the above studies, the mean age of the enrolled population in this study was lower, and there were fewer patients with hypertension, diabetes, heart failure, and atrial fibrillation. Our study confirmed that male sex and age were risk factors for all-cause death. A pre-

Table 2. Changes of echocardiographic indicators

	LVEF (%)	LVEDD (mm)	LVESD (mm)	LVEDV (mL)	LVESV (mL)
preoperative	57.71±12.63	48.75±9.07	32.48±9.33	109.97±54.15	50.75±41.44
follow-up	57.10±13.83	48.67±9.43	33.64±10.66	108.32±59.27	54.63±50.08
P	0.53	0.867	0.118	0.675	0.219

Note: LVEDD, Left Ventricular End Diastolic Diameter; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; LVESD, Left Ventricular End Systolic Diameter; LVESV, Left Ventricular End Systolic Volume.

Table 3. Changes of echocardiographic indicators by follow-up duration

	LVEF (%)	LVEDD (mm)	LVESD (mm)	LVEDV (mL)	LVESV (mL)
Follow-up less than 1 year (n=144)					
Preoperative	57.97±13.93	50.21±9.82	34.16±10.7	120.23±69.29	60.69±57.5
follow-up	57.07±13.32	49.12±9.31	34.66±11.65	112.92±60.14	57.42±52.3
P	0.345	0.147	0.779	0.273	0.288
Follow-up more than 1 year (n=316)					
Preoperative	57.59±12.01	48.09±8.64	31.71±8.54	105.29±44.97	46.22±30.59
follow-up	57.12±14.08	48.47±9.49	33.18±10.17	106.22±58.85	53.36±49.06
P	0.855	0.655	0.124	0.834	0.098

Note: LVEDD, Left Ventricular End Diastolic Diameter; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; LVESD, Left Ventricular End Systolic Diameter; LVESV, Left Ventricular End Systolic Volume.

vious study confirmed that diabetes and heart failure are independent predictors of all-cause death after pacemaker implantation [2]. In addition, the study excluded patients with short life expectancy, such as those with malignant tumors and consciousness disorders, which may have a definite impact on the final survival rate.

A Danish cohort of patients with complete atrioventricular block had a heart failure hospitalization rate of 11.3% at the 2-year follow-up after pacemaker implantation [10], similar to our findings. In this study, 90% of the patients with preoperative LVEF ≥ 50% still had a normal left ventricular function at follow-up, which strongly demonstrated that traditional pacemaker implantation had a good prognosis for patients with complete atrioventricular block and normal left ventricular function. However, different results have been observed in patients with reduced LVEF. A higher proportion of patients with reduced LVEF experienced deterioration of left ventricular function. A registered study on the effect of RV pacing on cardiac function showed that among patients with a baseline LVEF of 41-55%, 27.5% of patients with an RV pacemaker had a decrease in LVEF below 41% [11], similar to the results of this study. Simultaneously, improvement in left ventricular function was observed in some patients with reduced preoperative LVEF. The treatment of underlying diseases such as coronary artery disease and hypertension may benefit the improvement in left ventricular function in these patients. However, we did not identify a clear cause of cardiac dysfunction. In some patients, cardiac dysfunction may be caused by bradycardia, which can be corrected with a pacemaker. This suggests that in clinical practice, for patients with complete atrioventricular block and cardiac dysfunction, careful differentiation of the etiology of cardiac dysfunction and targeted treatment can avoid the need for CRT implantation. In patients with no improvement or deterioration in cardiac function after standard therapy, a meta-analysis showed that upgrading from a conventional pacemaker to CRT was similar to direct CRT implantation in terms of mortality and improved left ventricular remodeling [12].

Because of its closer proximity to the specialized conduction system, the RV septum is considered a more physiological pacing site than the RV apex. However, the results of clinical studies concerning left ventricular function have been conflicting. A meta-analysis concluded that non-RV apex pacing was more likely to have a better LVEF than RV apex pacing, with

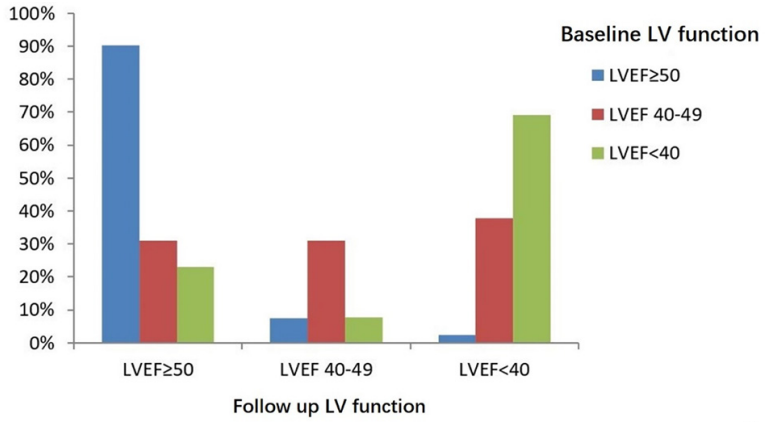

Figure 1. Echocardiographic follow-up of left ventricular ejection fraction (LVEF).

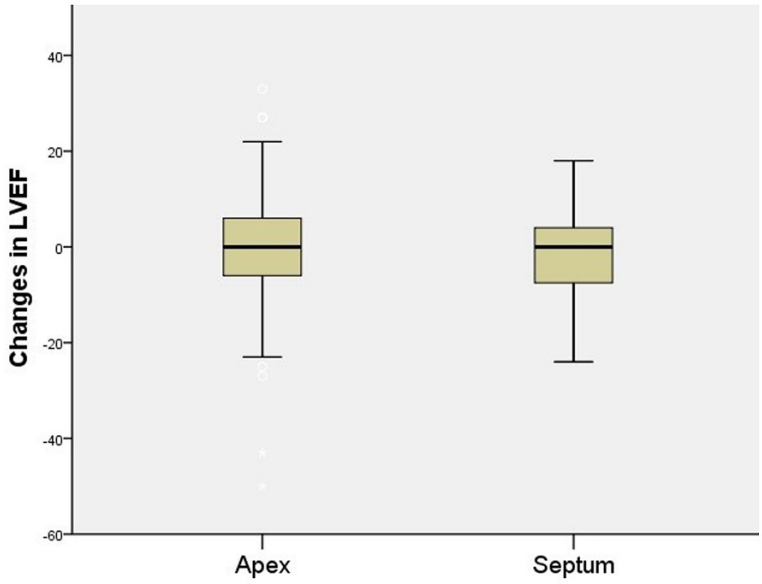

Figure 2. Changes in left ventricular ejection fraction (LVEF) by RV pacing lead site.

gested that an RV pacing burden of more than 20% was closely related to left ventricular remodeling [15]. Baseline left ventricular function has an important influence on the left ventricular response to RV pacing. A study using tissue Doppler to evaluate left ventricular synchronization showed that left ventricular dyssynchronization caused by RV pacing was greater when the baseline left ventricular function was reduced [16]. Therefore, guidelines recommend CRT implantation in patients with high-grade atrioventricular block and LVEF < 40% [1]. In patients with preserved left ventricular function, left bundle branch pacing (LBBP) was more beneficial than RV pacing when the a follow-up period longer than 12 months [13]. Two recent randomized studies suggested that RV septum pacing did not provide any protective effect on LV systolic function over RV apex pacing after 18 or 24 months of follow-up [6, 7]. In our study, after a median follow-up of 2.25 years, there were no statistically significant differences in LVEF changes between patients with RV pacing leads in the septum or apex, which is consistent with the above studies.

In the multivariate analysis, each percentage elevation in RV pacing was associated with a 5.3% increase in heart failure hospitalization. RV pacing can cause left ventricular contraction delay and an abnormal excitation sequence inside the left ventricle, resulting in reduced left ventricular filling volume and cardiac displacement. In the long term, ventricular asymmetry hypertrophy, ventricular dilation, and other cardiac remodeling phenomena occur, increasing the incidence of heart failure. The DAVID trial showed that an RV pacing burden of > 40% was associated with increased heart failure hospitalization [14]. Another study suggested that RV pacing burden was greater than 40% [17]. Although our study showed good results in a population where most patients retained left ventricular function, and we did not include LBBP as a comparison; further research is needed to determine the optimal strategy for patients with a high RV pacing burden.

Coronary artery disease was another independent predictor of heart failure hospitalization. As the primary cause of future deterioration in left ventricular function and myocardial fibrosis [18], studies have shown that in patients with myocardial fibrosis with an RV pacemaker, have more obvious left ventricular enlargement

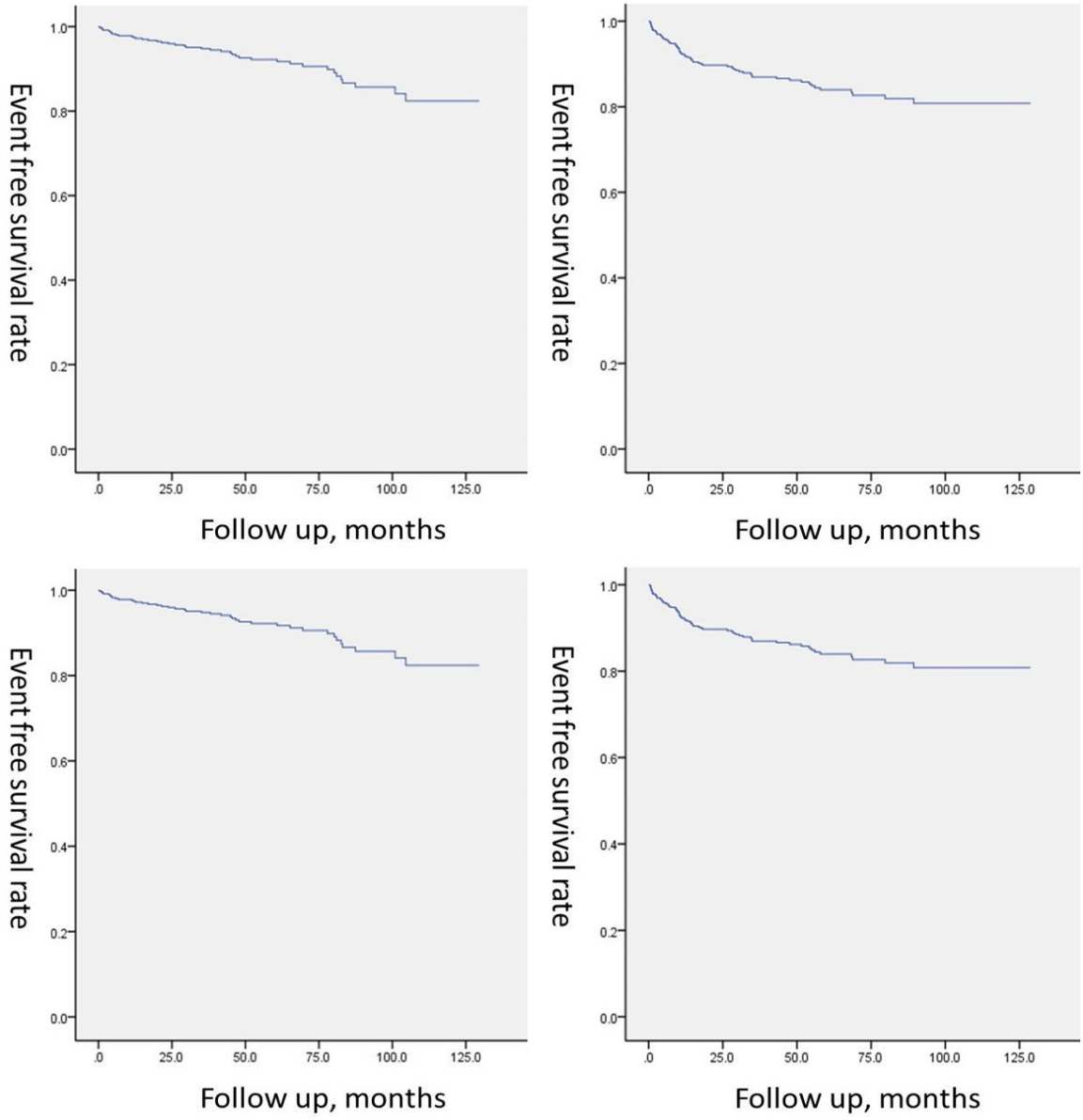

Figure 3. Cumulative survival without all-cause death (left), Cumulative survival without heart failure hospitalization (right).

Table 4. Multivariate analysis of predictors for clinical outcomes

	B	*S.E.*	*Wals*	*HR (95% CI)*	*P*
All-cause death					
Gender (Male)	0.993	0.365	7.408	2.698 (1.320-5.514)	0.006
Age	0.050	0.018	8.056	1.051 (1.016-1.088)	0.005
Heart failure hospitalization					
Age	0.025	0.012	3.957	1.025 (1.000-1.050)	0.047
Coronary artery disease	0.764	0325	5.541	2.148 (1.137-4.059)	0.019
LVEF	-0.031	0.010	8.511	0.970 (0.950-0.990)	0.004
RV pacing percentage	0.052	0.020	6.595	1.053 (1.012-1.096)	0.010

Note: LVEF, Left Ventricular Ejection Fraction; RV, Right Ventricular.

and left ventricular dysfunction which were observed during follow-up [19].

The major limitation of the present study was that we did not analyze left ventricular dyssynchrony using echocardiographic parameters. A previous study showed that RV pacing in the septum was associated with a less degree of dyssynchrony [20]. However, the relationship between echocardiographic dyssynchrony parameters and clinical outcomes remains to be proven. Another limitation is the lack of atrioventricular sequential pacing data. A study showed that dual-chamber pacing programmed for RV pacing, compared with continuous atrioventricular sequential pacing, resulted in more heart failure events [21].

Conclusion

This study showed that permanent pacemaker implantation in patients with complete atrioventricular block has a favorable long-term prognosis. Most patients with preoperative LVEF ≥ 50% had a normal left ventricular function at follow-up. Since RV pacing percentage is an independent predictor of heart failure hospitalization, patients with a high RV pacing burden require close follow-up.

Disclosure of conflict of interest

None.

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