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Original Article

Is right ventricular outflow tract pacing superior to right ventricular apex pacing? A long-term follow-up study

Xue Gong[1,4*], Yangang Su[2*], Yixiu Liang[2], Songwen Chen[3], Wenzhi Pan[2], Shaowen Liu[3], Hong Shen[1], Junbo Ge[2], Xianhong Shu[1]

Departments of [1]Echocardiography, [2]Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Disease, Shanghai 200433, China; [3]Department of Cardiology, Shanghai First People's Hospital, Shanghai, China; [4]Department of Cardiology, Deltahealth Hospital, Shanghai, China. [*]Equal contributors.

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Abstract: Background: We report the long-term results of our follow-up study, which compared right ventricular outflow tract (RVOT) pacing and right ventricular apex (RVA) pacing in terms of left and right ventricular function, synchrony, cardiac remodeling, the degree of valve regurgitation and clinical outcomes. Methods: Ninety-six patients with completed or high-degree atrio-ventricular block were prospectively enrolled and randomized to receive RVOT (group A, n=48) or RVA (group B, n=48) pacing.The follow-up were performed every 6 months in the first year, then every 1-2 years till the next implantation or for 8 years if the pacemaker was in normal condition. 2D, color Doppler, Tissue Doppler Imaging (TDI), and real-time three-dimensional echocardiography (RT3DE) were performed. Heart failure hospitalization and all-cause death rate were calculated. Results: Eighty-seven patients had extended follow-up, including 43 in group A and 44 in group B, with a mean duration of 7.0±1.0 years (3.1-8.3 years). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) in Group B were larger than those of group A (both $P<0.05$). There were no statistical differences of LVEF between the two groups. However, the mean myocardial systolic (Sm) and global longitudinal strain (GLS) of Group B were significantly lower than those of group A (both $P<0.05$). There were no statistical differences in the risk of hospitalization for heart failure and all-cause death rate. Conclusions: RVOT pacing had advantages in the protection of left ventricular systolic function and remodeling but was not superior to RVA pacing in valve regurgitation and clinical outcomes. Sm and GLS were sensitive in detecting early systolic dysfunction.

Keywords: Pacing, RVOT, RVA, left ventricle remodeling, outcomes research

Introduction

Traditional right ventricular apical pacemaker (RVA) has been widely used in clinical practice, because it is stable and easy to place. However, many recent studies have shown that RVA pacing may lead to left ventricular (LV) remodeling, deterioration of systolic and diastolic function, increased risk of heart failure and mortality [1-8].

These observations have displayed the need for other pacing modalities that allow for more physiological stimulation, such as RVOT, with good feasibility and reproducibility. Relevant studies concerning the comparison between ROVT and RVA had small sample sizes, were heterogeneous in patient characteristics and duration, and reached conflicting results. Also, the longest follow-up duration was only 1.5 years [9-11]. The one-year follow-up results of our research published in 2009 reached an almost negative conclusion [12]. Therefore, the question of whether RVOT pacing is superior to RVA pacing on long-term LV remodeling and clinical outcome is controversial. In consideration of the timing issues of pacing, it is worthwhile to evaluate the long-term impact of RVOT pacing and RVA pacing on clinical outcome, LV remodeling, LV systolic and diastolic function, and other echocardiographic parameters.

Methods

Study population

The patient characteristics, inclusion criteria, and one year follow-up results of our trial have

been published in detail previously [12]. In brief, this trial was a prospective, controlled clinical trial to determine whether RVOT pacing was superior to RVA pacing in preserving LV mechanical synchrony, systolic and diastolic function, avoiding LV remodeling among patients with normal cardiac function (LVEF≥55%) who had pacemaker implantation because of completed or high degree atria-ventricular block. As reported previously, patients were randomized into RVOT (Group A, n=48) or RVA (Group B, n=48) pacing group. In the RVA pacing group, the passive leads were positioned toward the right ventricular apex. In the RVOT pacing group, the active leads were positioned against the mid-septum of the RVOT, as in previous studies [12]. Our Ethics committee of Fudan University (Shanghai, China) approved the study and all patients signed informed consents.

Data acquisition and follow-up

Patients were enrolled between September 2006 and December 2007. The inclusion criterias were as follows: (1) the patients must be over 18 years of age; (2) the patients must have left ventricular ejection fraction (LVEF)≥55%; and (3) the patients must not have clinical manifestations of congestive heart failure. Follow-up examinations were performed every six months in the first year and, every one to two years after that. If the pacemaker was still effective eight years after implantation, an additional examination was performed. Echocardiography was performed within 24 hours before pacemaker implantation, at six months, one year, and at the last follow-up, using a commercially available system (Vingmed Vivid Seven, GE Vingmed, Milwaukee, WI) equipped with 3.5-MHz transducer. All echocardiographic examinations were performed and analyzed by the same experienced echocardiographer, who was blinded to clinical data and group division. 2D, Color Doppler, Tissue Doppler Imaging (TDI) were recorded to evaluate left and right ventricular function, left and right ventricular synchrony, cardiac remodeling, and the degree of valve regurgitation. Co-primary endpoints were LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LVEF, as measured by Simpson's rule, using 2D echocardiography. Secondary endpoints included heart failure hospitalization adjusted as the first hospitalization for heart failure and all-cause death rate. For assessment of systolic and diastolic synchrony, standard deviation of time to peak systolic of 12 segments (Ts-12SD) and time to peak early diastolic (Te-12SD) were measured, as they had changed at the one year follow-up. We also calculated Sm (mean myocardial systolic velocities of 12 segments) and Em (mean myocardial early diastolic velocities of 12 segments) to assess global LV systolic and diastolic function. Finally, we used 2D echo to measure left atrial diameter (LAD), color Doppler to evaluate mitral or tricuspid regurgitation (MR or TR), pulsed Doppler to measure changes in pulmonary artery systolic pressure (PASP), and M-mode echocardiography to measure tricuspid annulus plane systolic excursion (TAPSE). We use '+'~'++++' to express mild to severe MR or TR (+: the area of regurgitant jet is less than 4 cm^2, ++++: the area of regurgitant jet is over than 10 cm^2). Since the last follow-up, new technology has been introduced, including real-time three-dimensional echocardiography (RT3DE). In this study, 3D images were acquired and RT3DE was used to evaluate left ventricular function, including global longitudinal strain (GLS), global circumferential strain (GCS), and left ventricular synchrony, such as standard deviation of times to peak longitudinal strain of 16 LV segments (TIs16-SD), standard deviation of times to peak circumferential strain of 16 LV segments (Tcs16-SD), right ventricular function, such as right ventricular ejection fraction (RVEF), and right ventricular synchrony such as standard deviation of times to minimum systolic volume (Tmsv-sd) between the two groups.

Statistical analysis

Continuous data were presented as the mean ± SD, with the Kolmogorov-Smirnov test used to test the normality of the data. Categorical variables were compared with the Pearson X^2 test. A paired student t-test analysis was used for comparison within groups, a non-paired student t-test analysis for comparison between the two groups were performed as 2-sided tests. NYHA were compared with Fisher exact test. Heart failure hospitalization and event-free survival were calculated using Kaplan-Meier curves, which show log-rank X^2 values. A P value <0.05 was considered statistically

Table 1. Baseline characteristics of patients in the two groups at long-term follow-up

Parameters	RVOT pacing (n=43)	RVA pacing (n=44)	*P*-value
Age, years	68.68 ± 8.84	68.93 ± 9.71	0.907
Male sex, %	22 (51)	23 (52)	X^2=0.314 P=0.575
Base QRS duration, ms	96.68 ± 10.53	97.15 ± 10.23	0.840
Paced QRS duration, ms	151.10 ± 22.15	167.68 ± 24.33	0.002*
Cumulative percentage of Ventricular pacing (%)	97.4%	96.7%	0.72
Medical history, n (%)			
Hypertension	26 (60.5)	27 (61.4)	X^2=0.007 P=1.000
Diabetes mellitus	4 (9.3)	5 (11.4)	X^2=0.001 P=1.000
Coronary heart disease	3 (7.0)	3 (6.8)	X^2=0.188 P=1.000
Medications, n (%)			
Beta-blockers	3 (7.0)	5 (11.4)	X^2=1.49 P=0.26
ACE inhibitors or ARBs	20 (46.5)	16 (36.4)	X^2=0.63 P=0.51
Calcium channel blockers	10 (23.3)	14 (31.8)	X^2=1.09 P=0.34
Diuretics	4 (9.3)	3 (6.8)	X^2=0.13 P=1.000
Statins	6 (14.0)	4 (9.1)	X^2=0.40 P=0.74
Antiplatelet agents	9 (20.9)	4 (9.1)	X^2=2.15 P=0.23
Antiarrhythmic agents	3 (7.0)	2 (4.5)	X^2=0.188 P=1.000
NYHA function class I/II/III/IV	36/7/0/0	35/9/0/0	P=0.77

RVOT, right ventricular outflow tract; RVA, right ventricular apex; ACE, angiotensin-convertingenzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association. *P<0.05.

Table 2. Comparisons of primary endpoints measures between Group A and B

	Group A (n=43)		Group B (n=44)		P (Baseline vs Long-term)		P (Group A vs Group B)	
	Baseline	Long-term	Baseline	Long-term	Group A	Group B	Baseline	Long-term
LVEDV (ml)	80.68 ± 24.78	76.22 ± 19.61	81.55 ± 17.7	86.08 ± 19.38	0.103	0.105	NS	0.036*
LVESV (ml)	25.42 ± 10.64	24.73 ± 7.85	27.28 ± 7.77	30.48 ± 9.05	0.559	0.016#	NS	0.003*
LVEF (%)	67.85 ± 5.61	66.61 ± 4.37	68.10 ± 4.76	65.18 ± 5.99	0.296	0.006#	NS	0.221

Group A: RVOT pacing group; Group B: RVA pacing group. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction. *P<0.05 versus Group B; #P<0.05 versus baseline.

significant. All statistical analyzes were completed by using SPSS 19.0 software package (SPSS, Inc., Chicago, IL).

Results

Baseline characteristics

The baseline demographic data was shown in **Table 1**. The average follow-up duration was 7.0 ± 1.0 (3.1-8.3) years; 7.1 ± 1.1 (3.2-8.3) years in the RVOT pacing group and 6.9 ± 1.0 (3.1-8.2) years in the RVA pacing group. The cumulative percentage of ventricular pacing was 97.4% in the RVOT pacing group and 96.7% in the RVA pacing group. In the last follow-up, the New York Heart Association (NYHA) function classes of the groups were 35/4/4/0 in group A and 32/6/4/2 in group B (Fisher exact test, P=0.612). All parameters between the two groups were comparable before the pacemaker implantation.

Compliance with therapy

Among the study population of 96 patients, nine patients had a follow-up duration ≤ two years. Five patients in the RVOT group and four in the RVA group refused follow-up visits due to lack of symptoms.

Assessment of primary endpoints

In the RVA pacing group, LVEF was significantly decreased, and the difference between baseline and long-term follow-up was -2.9% (P=0.006). The corresponding changes in LVEF in the RVOT pacing group were -1.2% (P=0.296) (**Table 2**). However, there were no statistical dif-

Table 3. Comparisons of other 2D cardiac parameters between Group A and B

	Group A (n=43)		Group B (n=44)		P (Baseline vs Long-term)		P (Group A vs Group B)	
	Baseline	Long-term	Baseline	Long-term	Group A	Group B	Baseline	Long-term
Sm (cm/s)	4.64 ± 1.07	4.13 ± 0.98	4.82 ± 1.43	3.61 ± 1.12	0.000#	0.000#	NS	0.029*
Em (cm/s)	-5.81 ± 2.78	-4.37 ± 2.07	-5.35 ± 2.00	-3.88 ± 1.57	0.001#	0.000#	NS	0.235
Ts-12SD (ms)	27.09 ± 16.92	30.48 ± 13.36	30.23 ± 16.35	38.23 ± 16.47	0.109	0.003#	NS	0.022*
Te-12SD (ms)	22.24 ± 13.01	25.52 ± 9.90	22.51 ± 9.39	27.28 ± 1.76	0.130	0.017#	NS	0.452
LAD (mm)	36.80 ± 5.10	39.02 ± 4.58	37.85 ± 4.19	40.35 ± 4.85	0.001#	0.000#	NS	0.210
MR	0.68 ± 0.75	1.02 ± 0.71	0.75 ± 0.77	1.15 ± 0.70	0.006#	0.001#	NS	0.424
TR	0.65 ± 0.69	1.61 ± 0.94	0.80 ± 0.78	1.14 ± 0.85	0.000#	0.046#	NS	0.020*
PASP (mmHg)	18.73 ± 18.32	32.59 ± 12.48	20.95 ± 17.41	28.58 ± 17.07	0.000#	0.038#	NS	0.230
TAPSE (mm)	24.58 ± 3.12	21.05 ± 3.04	24.52 ± 3.00	20.80 ± 2.82	0.000#	0.000#	NS	0.704

Group A: RVOT pacing group; Group B: RVA pacing group. Sm: mean myocardial systolic velocities of 12 segments; Em: mean myocardial early diastolic velocities of 12 segments; Ts-12SD: standard deviation of time to peak systolic of 12 segments; Te-12SD: standard deviation of time to peak early diastolic of 12 segments; LAD: left atrial diameter; MR: mitral regurgitation; TR: tricuspid regurgitation; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annulus plane systolic excursion. *P<0.05 versus Group B; #P<0.05 versus baseline.

Table 4. Comparisons of RT3DE parameters in long-term follow-up between RVA and RVOT pacing group

	Group A (n=32)	Group B (n=31)	*P* value
GLS (%)	-19.02 ± 2.29	-17.71 ± 2.02	0.027*
GCS (%)	-30.36 ± 2.97	-29.84 ± 3.15	0.533
Tls16-SD	48.40 ± 19.40	42.89 ± 20.53	0.307
Tcs16-SD	56.95 ± 12.31	61.56 ± 14.29	0.200
RVEF (%)	57.54 ± 6.92	54.57 ± 7.51	0.130
Tmsv-sd	20.75 ± 11.32	31.62 ± 28.29	0.114

Group A: RVOT pacing group; Group B: RVA pacing group. GLS: global longitudinal strain; GCS: global circumferential strain; Tls16-SD: standard deviation of times to peak longitudinal strain of 16 LV segments; Tcs16-SD: standard deviation of times to peak circumferential strain of 16 LV segments; RVEF: right ventricular ejection fraction; Tmsv-sd: standard deviation of times to RV minimum systolic volume. *P<0.05 versus Group B.

ferences between the two groups at long-term follow-up (P=0.221). Three patients (6.8%) in the RVA group had LVEF≤55%.

Concerning the change in LVESV, there was a significant difference (P=0.003) between the two groups. Namely, LVESV increased from baseline to long-term follow-up with a difference of 3.20 mL in the RVA pacing group (P=0.016) (**Table 2**), while it slightly decreased by -0.69 mL in the RVOT pacing group (P=0.559) (**Table 2**).

At long-term follow-up, LVEDV was slightly increased with a difference of 4.53 mL (P=0.105) in the RVA pacing group and decreased by -4.46 mL (P=0.103) in the RVOT pacing group. The difference between the two groups was significant (P=0.036).

Assessment of other 2D and RT3D parameters

LAD and PASP in both groups increased significantly than baseline. Also, Sm, Em, TAPSE in both groups decreased significantly than baseline. MR and TR in both groups worsened than pre-operation, Ts-12SD and Te-12SD in Group B increased significantly than pre-operation (**Table 3**).

In the last follow-up, Sm of group B was lower than that of group A. TR in group A was significantly worse. However, there was no other differences between the two groups (**Table 3**).

Eleven patients from Group A and 13 patients from Group B had inadequate image quality for 3D analysis. There was no difference between two groups about RVEF and RV synchrony evaluated by RT3DE. GLS in group B was lower than that in group A (**Table 4**).

Assessment of secondary endpoints

Six patients in group B were hospitalized for heart failure (13.6%) while only three patients in group A (6.9%) were hospitalized. There was no statistical difference in the comparison of heart failure-free survival between the two groups (Chi-square test, P=0.484, Log-rank X^2=1.780, P=0.182) (**Figure 1**). There was no device or procedure-related deaths in either group. Two patients in group A died of cancer. In group B, one patient died of cancer, one patient died of renal failure, and two patients died of

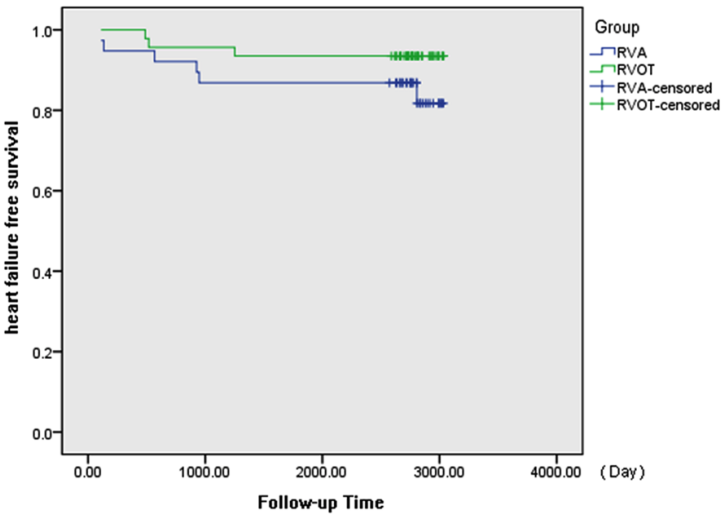

Figure 1. Comparison of heart failure-free survival between right ventricular apex (RVA) and right ventricular outflow tract (RVOT) pacing groups.

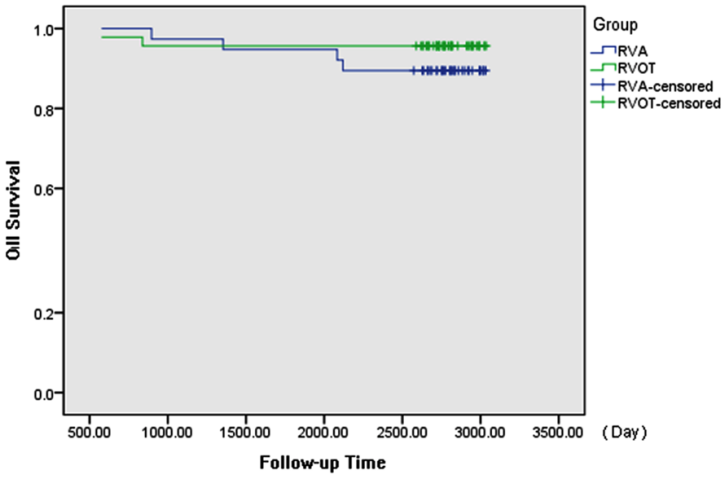

Figure 2. Comparison of overall survival rate between RVA and RVOT pacing groups.

heart failure. There were no statistical difference in the all-cause death rate (Chi-square test, P=0.676) and cardiovascular mortality (Chi-square test, P=0.494), the overall survival rate was no statistical different (Log-rank X^2= 1.096, P=0.295) (**Figure 2**).

Test-retest variability of LVEF, LVEDV, LVESV and parameters measured by RT 3DE

Inter-observer test-retest variability for measurement of LVEF, LVEDV and LVESV were within 4.2%, 5.7% and 5.9% respectively. Intra-observer variability for measurement of LVEF, LVEDV and LVESV were within 3.8%, 4.6% and 4.2% respectively.

Inter-observer test-retest variability for measurement of GLS, GCS, TIs16-SD, Tcs16-SD, RVEF and Tmsv-sd were 6.89%, 6.65%, 6.46%, 6.62%, 9.26% and 7.85% respectively. Intra-observer variability for measurement of GLS, GCS, TIs16-SD, Tcs16-SD, RVEF and Tmsv-sd were 5.85%, 5.72%, 6.32%, 6.58%, 7.62% and 6.89% respectively.

Discussion

This study was a long-term follow-up to our prospective, controlled study that compared the treatment efficacy of RVOT pacing and RVA pacing in patients with complete or high-degree AV block and normal LVEF. At long-term follow-up, the primary endpoints showed a reduction in LVEF in the RVA pacing group, but that there was no significant difference between the two groups. This conclusion correlated to that of the Protect-Pace study [11]. However, more sensitive parameters, such as Sm [13] and GLS, indicated that RVOT pacing had a protective effect on the LV systolic function though RVOT pacing did not protect the LV diastolic function.

As we know, the pathophysiological maladaptation of RVA pacing contributed to LV adverse remodeling, including LV enlargement, functional mitral regurgitation [14], and left atrial remodeling [15]. In this study, we found that LV adverse remodeling continued in the RVA pacing group and remained unchanged in patients who received RVOT pacing. LA remodeling was considered to be related to elevated filling pressures and impairment of LV systolic function [15]. However, in our study, LAD increased in both groups. This means that high proportions of long-term RVOT pacing also impaired LV systolic function to some extent and increased LV filling pressure. RVOT pacing did not show advantages in delaying LA remodeling.

Synchronization measurements reconfirmed that RVOT pacing can better maintain the heart

electro-mechanic synchrony than RVA pacing [12]. A previous study reported that early pacing-induced systolic dys-synchrony was closely related to the long-term LV remodeling and deterioration of LVEF [16]. Our study confirmed this conclusion. This might be caused by the development of systolic and diastolic dyssynchrony through separate mechanisms [17, 18].

In our study, different from the conclusion by Hemayat S et al [14], MR and TR of both groups worsened between pre-operation and long-term follow-up. Increased TR resulted in right heart overload and increased PASP. TR induced by RVOT pacing was more evident. A possible reason may be that the active lead, which first passed through the tricuspid valve (TV) and lead to the RVOT septum, formed an angle with the TV, making it more likely to cause tricuspid insufficiency.

Our study first evaluated the effect of different pacing mode on RV function. We found that the TAPSE of the two groups decreased post operation, but it was still in the normal range. There was no difference between the two groups, as with the RT3DE parameters. This means that a high proportion of long-term pacing increased the RV load, which was influenced by TR, and finally affected the RV function.

Although LVEF in the RVA group was obviously decreased, it remained in the normal range. The risk of heart failure was low in both groups, coming to the same conclusion with Sweeney and Hellkamp [19]. There were no statistical differences in terms of hospitalization for heart failure and long-term survival, which means that long-term RVA pacing was also safe in patients with normal LV systolic function [20].

Overall, for a high proportion of long-term ventricular pacing, RVOT pacing is superior to RVA pacing in improving LV systolic synchronization, delaying LV remodeling and protecting LV systolic function. However, it is no better than RVA pacing in reducing valve regurgitation, improving LV diastolic and RV systolic synchronization, protecting LV diastolic function and RV function.

The results of our study show that for patients with normal cardiac function, about seven years of sustained ventricular pacing did not lead to obvious left ventricular dysfunction. RVOT pacing had an advantage in the protection of left ventricular systolic function and remodeling but was no better than RVA pacing in the clinical outcomes. Sm and GLS were sensitive in detecting early systolic dysfunction.

Study limitations

A limitation of this study was the relatively small sample size. However, the size of the sample had adequate statistical power to show differences in the primary endpoints. Another limitation of this study was the issue of timing of echocardiograms, only the samples taken pre-operation and last follow-up post-operation were compared. No intervening samples were used in this study which means we cannot be certain when the parameters were changed. However, this does not affect the conclusion of this study in any way.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xianhong Shu, Department of Echocardiography, Zhongshan Hospital, Fudan University, 180 Feng Lin Road, Shanghai 200032, China. E-mail: shu.xianhong@zs-hospital.sh.cn; Dr. Junbo Ge, Department of Cardiology, Zhongshan Hospital, Fudan University, 180 Feng Lin Road, Shanghai 200032, China. Tel: +86-21-64041990-8509; Fax: +86-21-64223006; E-mail: ge.junbo@zs-hospital.sh.cn

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