

Long-Term Follow-up Impact of Dual-Chamber Pacing on Patients with Hypertrophic Obstructive Cardiomyopathy

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[Correction added after online publication 24-October 2012. Hu Yue-Cheng and Li Zuo-Cheng listed as co-authors.]

Background: Pacing has been proposed as a treatment for patients with hypertrophic obstructive cardiomyopathy (HOCM), but there are few studies with long-term follow-up. We evaluated the long-term effects of dual-chamber pacing therapy for patients with HOCM, and to identify the most prognosis-specific factors for predicting outcome in such treating methods.

Methods: A total of 37 HOCM patients implanted with dual-chamber pacemakers were enrolled consecutively and followed-up. Thirty-seven cases were followed for 1 year, 26 cases for 2 years, 10 cases for 3 years, and eight cases for 4 years. At each annual point of follow-up after pacemaker implantation, the pacing frequency, pacing threshold, impedance, atrioventricular delay, and cumulative percentage of atrial and ventricular pacing were tested, respectively. In addition, left atrial dimension (LAD), left ventricular end diastolic dimension (LVEDd), left ventricular posterior wall thickness (LVPW), interventricular septum thickness (IVS), left ventricular outflow tract dimension (LVOTd), peak velocity of left ventricular outflow tract (VLVOT), left ventricular outflow tract pressure gradient (LVOTPG), left ventricular ejection fraction (LVEF), and pulmonary artery systolic pressure (PASP) were measured. Mitral valve systolic anterior motion (SAM) was also observed. Pacing parameters and echocardiography indexes before and after pacemaker implantation were dynamically compared.

Results: Pacing frequency and atrioventricular delay were adjusted to 60–70 beats per minute and 90–180 ms, respectively, in order to ensure the ratio of ventricular pacing was more than 98%. Pacing threshold and pacing impedance were kept in normal ranges. The differences of various pacing parameters were of no statistical significance within the 4 years of follow-up ($P > 0.05$). Compared with prior to pacing, it was observed that the IVS, VLVOT, and LVOTPG declined significantly ($P < 0.01$), the LVOTd widened significantly ($P < 0.01$), and the SAM phenomenon improved obviously ($P < 0.01$) at 1, 2, 3, and 4 years after pacemaker implantation. Additionally, the changes in LAD, LVEDd, LVPW, LVEF, and PASP were statistically insignificant ($P > 0.05$).

Conclusions: The cardiac structural reconstruction in patients with HOCM can be chronically improved by dual-chamber pacing therapy. The IVS, LVOTd, VLVOT, and LVOTPG can be used as sensitive and specific factors in evaluating the long-term effects of dual-chamber pacing therapy for HOCM. (PACE 2013; 36:86–93)

cardiomyopathy, hypertrophic, pacemaker, echocardiography, follow-up studies

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM), as an autosomal dominant disease,

is characterized by pathological, asymmetric left ventricular hypertrophy and left ventricular outflow tract obstruction. Currently, therapeutic measures include medication, surgery, ablation, and pacing. Permanent dual-chamber pacing has been proposed as an adjunct treatment to reduce symptoms in markedly symptomatic patients with HOCM.^{1–4} Whereas several early observational and uncontrolled studies have suggested that atrial-synchronous ventricular pacing may markedly reduce outflow gradient and symptoms,^{1–4} other more recent investigations have yielded less uniform, more heterogeneous results and skepticism.^{5–9}

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Received April 22, 2012; revised July 18, 2012; accepted August 14, 2012.

doi: 10.1111/pace.12016

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Although there have been many studies on pacing therapy for HOCM, there are few studies with 4 years follow-up. Our study consecutively followed HOCM patients who accepted the dual-chamber pacemaker implantation, observed the dynamical changes of pacing parameters and echocardiography indexes for 4 years after the implantation, then evaluated the long-term effects of dual-chamber pacemaker implantation. Furthermore, we have identified and discussed the most sensitive and specific echocardiography indexes that we observed in assessing the long-term effects of pacing to improve, if not cure, HOCM.

Methods

Patients

Over a 4-year period (Jan. 2007 to Jan. 2012), 37 patients with HOCM, who were admitted to our hospital and had accepted the dual-chamber pacemaker implantation, were enrolled and followed-up consecutively.

Each patient fulfilled the following entry criteria: (1) Unequivocal diagnosis of hypertrophic cardiomyopathy (HCM) on the basis of two-dimensional echocardiographic demonstration of a hypertrophied (wall thickness ≥ 15 mm) and nondilated left ventricular (LV) in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy present; (2) pressure gradient between left ventricular outflow tract and aorta of ≥ 30 mm Hg under resting conditions, estimated by continuous wave Doppler^{10,11}; (3) patients were unsuitable or tried drugs with no effect or they were intolerant to medication with β -blocker or calcium channel blocker.

Entry exclusions included chronic atrial fibrillation (AF), left bundle branch block, end-stage phase of HCM,¹² prior septal myotomy-myectomy operation,^{13–17} systemic disease that would preclude completion of the protocol, and contraindications to (or established indications for) permanent pacing.

Overall, 37 cases were followed for 1 year, 26 cases for 2 years, 10 cases for 3 years, and eight cases for 4 years; only one patient died from sudden cardiac death 2 years after pacemaker implantation. The study was approved by the medical ethics committee of Tianjin Chest Hospital. All patients provided written informed consent, and the study was carried out in accordance with the Declaration of Helsinki.

Study Design

Left subclavian vein puncture was performed on all of the patients, followed by dual-chamber

pacemaker implantation. The atrial lead was fixed in the auricle of the right atrium and the ventricular lead in the apex of the right ventricle. Rate response was programmed off. Pacing parameters such as threshold, impedance, and sensing tested during the operation satisfied the pacemaker implanting criteria.

Follow-up was performed annually for 4 years after pacemaker implantation to collect the data including pacing frequency, pacing threshold and impedance, atrioventricular delay, and cumulative percentage of atrial and ventricular pacing. During data collection, all patients lay in the left lateral position with quiet breathing and were investigated using the Philips iE33 diagnostic ultrasound scanner (Philips Healthcare, Best, the Netherlands) and ultrasound transducers S5–1 with the frequency of 1.7–3.4 Hz. The data were measured using the M-mode and two-dimensional echocardiogram at end-diastole in 50–80 frame/frame frequency conditions. Measurements included left atrial dimension (LAD), left ventricular end-diastolic dimension (LVEDd), left ventricular posterior wall thickness (LVPW), interventricular septum thickness (IVS), left ventricular outflow tract dimension (LVOTd), and pulmonary artery systolic pressure (PASP). Systolic mitral valve systolic anterior motion (SAM) was observed. Left ventricular ejection fraction (LVEF) was measured through double-plane Simpson's, peak velocity of left ventricular outflow tract (VLVOT) was measured with continuous wave Doppler, and left ventricular outflow tract pressure gradient (LVOTPG) was calculated by the Bernoulli equation.

Statistical Analysis

It was performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). Continuous data were reported as mean \pm standard deviation, and the differences within groups were analyzed by the *t*-test of paired-samples. Categorical data were presented as percentages, and analyzed by the Chi-square test. A *P* value of <0.05 (two-sided) was considered statistically significant.

Results

Patient Description

The patients' ages ranged from 34 to 71 years (mean 52 ± 21); 17 (46%) were female. All patients presented with one or more symptoms of exertional dyspnea (76%), palpitations (70%), angina pectoris (52%), and syncope (31%). The symptoms had been present for 8 (± 4.4) years. Four (11%) patients were in New York Heart Association functional class I, 26 (70%) were

class II/III, and seven (19%) were class IV. All patients were unsuitable because of bradycardia or tried drugs but no effect or intolerant to medication with β -blocker or calcium channel blocker. Several months (mean 2.4 ± 0.3) after the pacemaker implantation, the symptoms referred were obviously improved.

Follow-up of Pacing Parameters within 4 Years after Dual-Chamber Pacemaker Implantation

The mode of cardiac pacing for every patient was DDD. The patients' automatic heart rate ranged from 54 to 87 beats per minute (bpm), with an average of (62 ± 10.4) bpm, which included five patients (about 13.5%) with paroxysmal atrial fibrillation. During the follow-up, the lower limit of pacing frequency was adjusted to 60–70 bpm, and atrioventricular delay to 90–180 ms, in order to make the ratio of ventricular pacing more than 95%; pacing threshold and pacing impedance of atrium and ventricle were kept in normal ranges. Differences of various pacing parameters were statistically insignificant ($P > 0.05$). The result of pacing parameters is shown in Table I.

Follow-up of Echocardiography Parameters 4 Years after Dual-Chamber Pacemaker Implantation

Compared with prepacing, at the time of 1, 2, 3, and 4 years after pacemaker implantation, the IVS, VLVOT, and LVOTPG declined significantly ($P < 0.01$); the LVOTd widened significantly ($P < 0.01$); and the SAM phenomenon improved significantly ($P < 0.01$). However, the changes in LAD, LVEDd, LVPW, LVEF, and PASP were not statistically significant ($P > 0.05$). The result of echocardiography parameters is shown in Table II; variation trends of IVS, LVOTd, VLVOT, and LVOTPG after operations are shown in Figures 1–4.

Discussion

The characteristic of HOCM is marked by asymmetric hypertrophy in different areas of the left ventricle, especially in the areas of the interventricular septum and the posterior wall of the left ventricle. Both the systolic and diastolic functions are impaired. Severely symptomatic patients refractory to drug therapy with marked obstruction to left ventricular outflow constitute a small but important subset of patients with hypertrophic cardiomyopathy. During the systolic period the hypertrophic interventricular septum protrudes into the left ventricular outflow tract and the anterior mitral valve leaflet moves forward, causing the left ventricular outflow tract to become narrowed or obstructed; this is termed the SAM of the mitral valve. This is followed by cardiac

Table I.
The Result of Pacing Parameters during Follow-up

Group	n	Pacing Frequency (bpm)	Atrioventricular Delay (ms)	Pacing Threshold of Atrium (mV)	Pacing Threshold of Ventricle (mV)	Pacing Impedance (Ω)	Ratio of Atrial Pacing (%)	Ratio of Ventricular Pacing (%)
Point of implantation	37	63.4 ± 10.6	120.2 ± 21.4	0.6 ± 0.3	0.5 ± 0.6	534 ± 72	—	—
One year after implantation	37	65.2 ± 9.8	112.6 ± 23.1	0.6 ± 0.4	0.6 ± 0.1	563 ± 69	87.2 ± 12.4	98 ± 2.5
Two years after implantation	26	66.1 ± 11.1	109.3 ± 26.5	0.6 ± 0.6	0.7 ± 0.2	573 ± 97	90 ± 14.6	98 ± 2.1
Three years after implantation	10	64.3 ± 12.3	114.7 ± 25.8	0.7 ± 0.2	0.7 ± 0.8	604 ± 117	88 ± 13.1	99 ± 0.7
Four years after implantation	8	65.7 ± 14.6	106.4 ± 24.5	0.7 ± 0.6	0.6 ± 1.2	598 ± 122	93 ± 12.4	98 ± 1.8

Data are expressed as mean \pm standard deviation values.

Table II.
The Result of Echocardiography Indexes during Follow-up

Time of Follow-up	n	LAD (mm)	LVEDd (mm)	LVPW (mm)	IVS (mm)	LVOTd	VLVOT (m/s)	LVOTPG (mm Hg)	LVEF (%)	PASP (mm Hg)	SAM n (%)
One year after implantation	37										
Pre		40.6 ± 5.6	48.1 ± 8.3	13.3 ± 3.8	29.2 ± 4.1	23.2 ± 4.7	4.2 ± 1.2	62.1 ± 10.7	64.2 ± 11.7	36.5 ± 6.4	31(79.5)
Post		42.7 ± 6.1	47.1 ± 6.7	12.1 ± 3.2	27.4 ± 3.7	25.1 ± 4.7*	3.4 ± 1.3*	43.7 ± 8.8*	67.2 ± 12.5	37.8 ± 6.6	13(35.1)*
Two years after implantation	26										
Pre		39.7 ± 5.1	50.3 ± 7.9	14.3 ± 3.7	28.2 ± 6.1	24.1 ± 4.2	4.0 ± 1.1	60.8 ± 13.2	66.3 ± 12.0	34.6 ± 7.1	21(80.8)
Post		43.1 ± 7.7	51.2 ± 6.4	12.3 ± 2.8	22.4 ± 5.6*	26.5 ± 5.2*	3.1 ± 0.9*	42.2 ± 9.3*	65.2 ± 14.3	35.4 ± 6.8	8(30.8)*
Three years after implantation	10										
Pre		40.5 ± 4.7	49.3 ± 7.2	13.8 ± 3.4	29.6 ± 7.2	24.6 ± 4.3	4.2 ± 1.2	63.3 ± 11.6	64.8 ± 12.6	35.7 ± 6.9	8(80)
Post		42.1 ± 5.7	50.6 ± 6.6	12.1 ± 3.0	20.8 ± 5.5*	28.2 ± 4.4*	2.8 ± 0.8*	39.4 ± 6.8*	65.7 ± 13.4	36.7 ± 7.4	3(30)*
Four years after implantation	8										
Pre		40.9 ± 4.5	48.9 ± 6.9	13.1 ± 3.9	30.1 ± 7.4	24.1 ± 4.8	4.1 ± 1.3	62.1 ± 12.4	63.3 ± 13.4	34.6 ± 7.5	7(87.5)
Post		41.7 ± 5.2	50.1 ± 7.1	12.4 ± 4.1	21.1 ± 6.1*	28.7 ± 4.9*	2.7 ± 1.1*	38.7 ± 7.1*	64.9 ± 12.3	35.6 ± 7.9	2(25.0)*

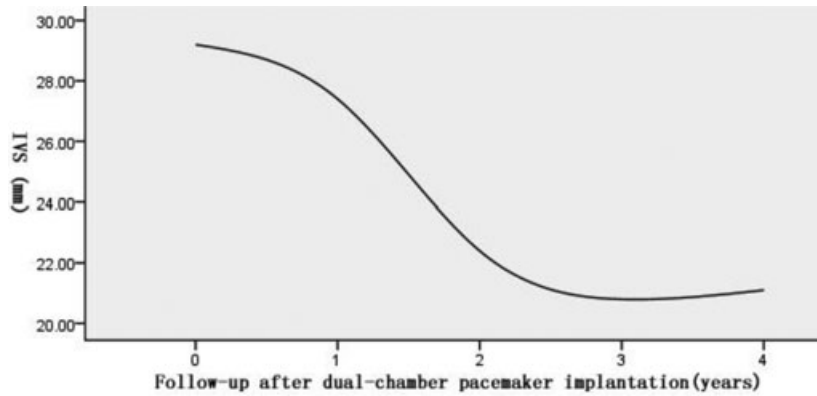


Figure 1. Variation trend of IVS over 4 years postimplantation.

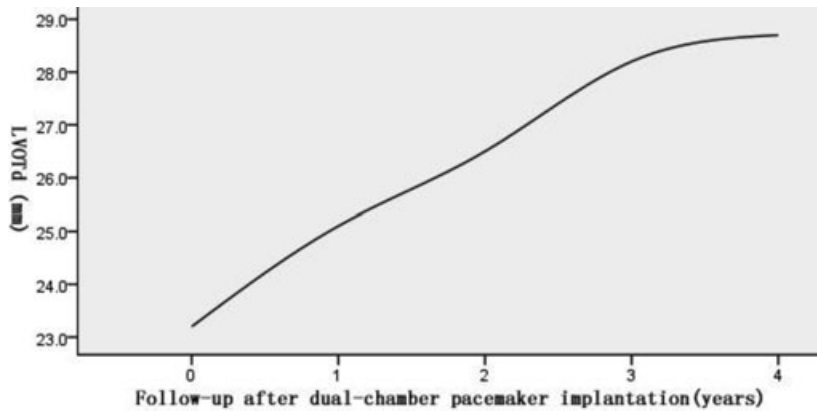


Figure 2. Variation trend of LVOTd over 4 years postimplantation.

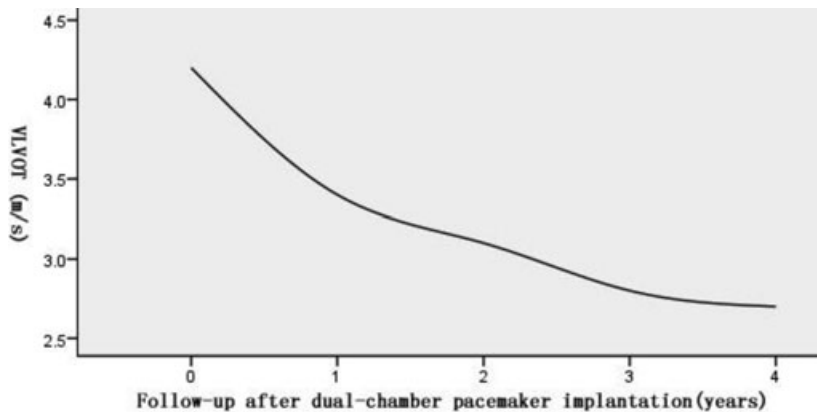


Figure 3. Variation trend of VLVOT over 4 years postimplantation.

muscle denaturation, apoptosis, and fibrosis, with the final outcome being left ventricular dilatation or functional declined and congestive heart failure. Initially, HOcm involves IVS thickening causing the LVOTd to decrease. Hemodynamically, this leads to VLVOT acceleration, eventual LVEDd increase, and a reduced LVEF. Hence, it is

assumed that a reverse in the changes of these parameters with the disappearance of the SAM phenomena shown by echocardiography indicates improvement in the pathophysiology of HOcm.

Current therapies for HOcm include medication, surgery, ablation, and pacing. For almost 50 years, the ventricular septal myotomy-myectomy

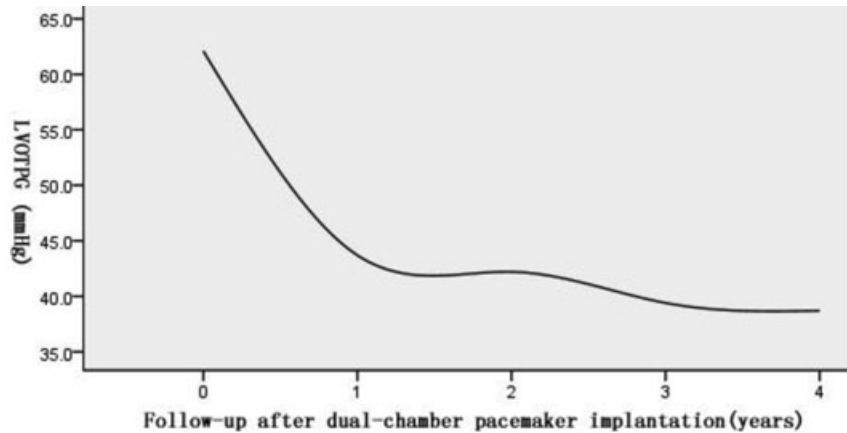


Figure 4. Variation trend of LVOTPG over 4 years postimplantation.

operation has been the standard surgical therapeutic option for these patients and has provided substantial symptomatic benefit with relief of outflow obstruction associated with low operative mortality.^{13–16} However, there are relatively few surgical centers with sufficient experience in these operative techniques and as a result, many patients may not have ready access to this treatment option. In addition, some patients, such as the elderly, may not be ideal operative candidates.¹⁸ Compared with nonpacing treatments, pacing therapy is easier to perform and much less invasive. It is especially beneficial for patients with impaired cardiac conduction systems as the full dose of medication can still be prescribed.

Dual-chamber pacemaking results in significant benefits for patients with high-pressure gradients of the left ventricular outflow tract (LVPG) and severe symptoms, especially the elderly. M-PATHY tests indicate that pacing therapy has significant effects on HOCM patients older than 65-years of age.¹⁹ According to the guidelines of the American College of Cardiology/American Heart Association/Heart Rhythm Society in 2008 for device-based therapy of cardiac rhythm abnormalities,²⁰ permanent pacing is indicated for sinus node dysfunction or atrioventricular block in patients with HCM (Class IC), and recommendations for pacing in patients with hypertrophic cardiomyopathy, permanent pacing may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow tract obstruction (Class IIb), and permanent pacemaker implantation is not indicated for patients who are asymptomatic or whose symptoms are medically controlled or symptomatic patients without evidence of LV outflow tract obstruction (Class IIIc). As a progressive disease, especially for the patients who have suffered from syncope episodes, the

mortality rate of HOCM is up to 4%–6% per year.⁵ Our follow-up shows that the survival rate at 3-year follow-up after dual-chamber pacemaker implantation was 97.3%, hence greatly improving the outcome of HOCM.

In our research, echocardiography results of HOCM patients showed that following dual-chamber pacemaker implantation, the IVS gradually decreased, LVOTd gradually increased, VLVOT and LVOTPG decelerated, and the SAM phenomenon disappeared without changes of LVEDd and LVEF. In addition, left ventricular outflow tract obstruction was lightening and hemodynamics was improved markedly. The mechanisms resulting in the improvements are: (1) Proper implantation location of the ventricular lead. The ventricular lead was fixed in the apex of right ventricle. The ventricular activation site of origin should be the apex of right ventricle, resulting in excitation of the interventricular septum prior to the remainder of the ventricle, contracting in advance and moving away from the left ventricular outflow tract. This makes the left ventricular outflow tract gradient pressure lower and alleviates the anterior movement of mitral valve in the systolic period. Furthermore, it reduces the outflow tract obstruction, increases the cardiac output, and improves the clinical symptoms.²¹ Previous studies have shown that right ventricular apical pacing could reduce the outflow tract gradient by a mean of 58 mm Hg, compared to high-septal pacing where the outflow tract gradient was not reduced.²² (2) The mitral valve plays an important role in the dynamic obstruction; its motion may be modified by pacing and reversing the normal base to apex activation. Pacing activation of the right ventricular apex could produce early activation of the papillary muscles and chordae, which could limit mitral valve leaflet excursion. It is possible

that premature apical tensing of the mitral valve and early tensing of the chordae of the mitral valve may reduce SAM by mitigating excess slack.²³ (3) Selected mode of cardiac pacing. At first VVI was chosen; however, it reduced the outflow tract gradient which brought blood pressure down by 13% and decreased cardiac output by 30%. It is also associated with several side effects such as pacemaker syndrome.²⁴ VDD mode has been investigated in some studies as it could improve the clinical symptoms in patients with HOCM to some extent. Recently studies have focused on DDD mode such as in the study conducted by Fananapazir et al.⁴ DDD devices were implanted in 84 patients with HOCM, at a mean follow-up of 2.3 ± 0.8 years. The total effective rate was 89% with a cumulative 3-year survival rate of 97% and echocardiography demonstrating significant reductions in left ventricular outflow tract gradient. (4) Pacemaker programming of parameters including atrioventricular delay and pacing frequency. Optimal atrioventricular delay ensures ventricular capture and favorable atrioventricular contracting sequence, shortens the ventricular peak filling time, and reduces the preload of the heart. An investigation indicated that the best effects could be achieved when atrioventricular delay was controlled at a mean value of 100–120 ms resulting from notable reduction of left outflow tract gradient with no impairment of left ventricular end-diastolic pressure and cardiac output.² Heart rate is an important independent risk factor that influences the hemodynamics in the pacing therapy of HOCM. With heart rate elevation, the DDD pacing mode can reduce the left ventricular outflow tract gradient significantly. We regulated the lower heart rate at 60–70 bpm and the upper at 150 bpm. In order to reduce the

outflow tract gradient continuously and improve symptoms during pacemaker therapy, the right ventricle should be excited as early as possible and cumulative percentage of ventricular pacing should be higher than 95%.⁵

The mechanics of pacing therapy for HOCM patients are complicated. Only through appropriate selection of pacing mode specific to hypertrophic cardiomyopathy, close follow-up of the pacing parameters, making appropriate adjustments when necessary, and assessing the therapeutic effects using echocardiography, can the optimal results of pacing therapy be achieved. Currently, there are few indexes used to evaluate the pacing effects in patients with HOCM. Our research was able to show that the IVS, LVOTd, and VLVOT could be used as both sensitive and specific echocardiographic indexes to assess the long-term effects of dual-chamber pacing to improve outcomes in patients with HOCM.

Limitations

This study was single center's retrospective clinical study with small patient population from China. Therefore the data had their own limitations. The findings and its application should be confirmed and validated in a large multicenter trial before being widely used.

Conclusion

1. The cardiac structural reconstruction in patients with HOCM can be chronically improved by dual-chamber pacing therapy.

2. The IVS, LVOTd, VLVOT, and LVOTPG can be used as sensitive and specific factors in evaluating the long-term effects of dual-chamber pacing therapy for HOCM.

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