Long-term Effect of Dual-chamber Pacing on Pressure Gradient at Left Ventricular Outflow Tract in Hypertrophic Obstructive Cardiomyopathy

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A 60-year-old man with hypertrophic obstructive cardiomyopathy (HOCM) was implanted dual-chamber ICD for the purpose of both the left ventricular outflow tract (LVOT) gradient reduction by ventricular pacing and the primary prevention of ventricular tachyarrhythmia. Because the LVOT gradient reduction and improvement of symptoms by pacing were insufficient, however, a new pacing lead was inserted in the right ventricular apex at a different position 1.5 cm away from the site of the defibrillation lead, and the LVOT gradient greatly declined from 108 to 30 mmHg. This DDD pacing was continued over seven years. On this occasion, he was referred to our hospital because of battery depletion, and a cardiac catheterization study was performed after ICD replacement. The LVOT gradient was 10 mmHg in sinus rhythm. After administration of isoproterenol (0.02 μg), the gradient was increased to 92 mmHg in sinus rhythm. DDD pacing using a newly placed ventricular pacing lead significantly decreased the gradient to 36 mmHg. This case study indicated that DDD pacing from a suitable location in the right ventricular apex caused a marked early reduction in the LVOT gradient, and at long-term follow up a further significant effect was obtained, also in sinus rhythm.

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Introduction

Hypertrophic cardiomyopathy (HCM) is a disorder characterized by the presence of otherwise unexplained ventricular hypertrophy. The prevalence of HCM in the general population is estimated to be as high as 0.2%, and about 25% of cases present with septal hypertrophy, leading to dynamic obstruction of the left ventricular outflow tract (LVOT), which is called hypertrophic obstructive cardiomyopathy (HOCM). A pressure gradient at the LVOT of more than 50 mmHg is a powerful predictor of an adverse
outcome. There are several types of treatment in patients with HOCM whose condition is refractory to medical therapy, such as septal myotomy and myectomy, transcoronary alcohol ablation of the interventricular septum, and dual-chamber pacing. Recently, the beneficial effect of dual-chamber (DDD) pacing to reduce the LVOT gradient has been well documented in patients with HOCM. It has not been established, however, whether the initial favorable effect of DDD pacing is maintained long term. In addition, there are few reports about the LVOT gradient reduction measured in sinus rhythm at late follow-up. Here, we report a HOCM case in which DDD pacing from a suitable site in the right ventricular apex decreased the LVOT gradient greatly with implantable cardioverter defibrillator (ICD) implantation, and continuous DDD pacing over seven years significantly decreased its level further, also in sinus rhythm.

Case Report
Clinical Course
In November, 1999, a 60-year-old man was seen at another hospital because of palpitations, and paroxysmal atrial fibrillation and HOCM were diagnosed on echocardiography. The pressure gradient at the LVOT was 58 mmHg at rest. In April and July, 2002, he was admitted to our hospital with pulmonary edema, although he had been taking cibenzoline 300 mg, verapamil 240 mg, and atenolol 50 mg. At that time, the thickness of the interventricular septum was 20 mm on echocardiography, and a cardiac catheterization study revealed that LVOT gradient was 108 mmHg and ventricular tachycardia was induced by ventricular extrastimulus testing. His condition was refractory to medical therapy, and accordingly on August 30, 2002, a dual-chamber ICD was implanted intravenously to reduce the LVOT gradient by ventricular pacing, as well as for the primary prevention of ventricular tachyarrhythmia. The atrial pacing lead was located in the right atrial appendage, and the defibrillation lead was located in the right ventricular apex. However, the LVOT gradient reduction and improvement of symptoms were insufficient by pacing under any atrio-ventricular delay conditions. On September 13, 2002, a new pacing lead was inserted in the right ventricular apex at a different position 1.5 cm away from the site of the defibrillation lead, and as a result the LVOT gradient greatly declined from 108 to 30 mmHg under the conditions of DDD pacing rate 70/min, sensed AV delay 80 ms and paced AV delay 120 ms. The newly inserted pacing lead played the role of pacing and the formerly inserted defibrillation lead only the role of treating the ventricular tachyarrhythmia. DDD pacing was continued and the patient’s condition remained good over seven years, and on this occasion, he was referred again to our hospital for ICD replacement because of battery depletion.

Findings on admission
The patient had no family history of HCM. Blood pressure was 126/60 mmHg and pulse rate was 60 beats/min and regular. Physical examination revealed a mid systolic heart murmur of Levine 2/6 along the left sternal border. Brain natriuretic peptide (BNP) level was 237 pg/ml. Twelve-lead electrocardiogram showed p-tracking ventricular pacing. Chest X-ray showed the ICD implanted in the upper left anterior portion of the chest with an atrial pacing lead, a ventricular defibrillation lead and a ventricular pacing lead.

Cardiac Catheterization study
Accordingly, after replacement of the ICD, a
cardiac catheterization study was performed under the conditions of DDD pacing rate 70/min, sensed AV delay 80 ms and paced AV delay 120 ms. The left ventricular apex pressure using a multipurpose catheter and aortic pressure using a pigtail catheter were recorded simultaneously and the pressure difference was used as a surrogate endpoint of the LVOT gradient. At first, DDD pacing was turned off, and observation was continued over 60 minutes. The LVOT gradient was 10 mmHg in sinus rhythm, and changed little during DDD mode pacing (Figure 2).

After administration of isoproterenol (0.02 \(\gamma\)), maximum heart rate was increased to 80/min, and the LVOT gradient was increased to 92 mmHg in sinus rhythm. During DDD pacing using the defibrillation lead for ventricular pacing, the gradient decreased to 62 mmHg, and by use of the additionally inserted ventricular pacing lead, it significantly decreased to 36 mmHg (Figure 3).

**Discussion**

**HOCM and effect of pacing**

It has been known for about 30 years that right ventricular apex pacing can reduce the LVOT gradient in HOCM. The M-PATHY study (Multi-center Study of Pacing Therapy for Hypertrophic Cardiomyopathy) involved 48 patients and showed a reduction in the LVOT gradient in those with a DDD pacemaker (from 82 to 48 mmHg, \(P < 0.001\)), which, however, was not associated with improvement in functional capacity.\(^6\) The PIC (Pacing in Cardiomyopathy) study involved 83 patients and found that those patients randomized to receive a DDD pacemaker had a significant reduction in LVOT gradient (from 72 to 29 mmHg) and an improvement in symptoms and functional capacity.\(^7\) Megevand et al. have reported a study of DDD pacemaker implantation in HOCM with long-term follow up (up to 10 years);\(^8\) They found a statistically significant reduction in LVOT gradient that was maintained and more apparent over time (from 82 to 42 mmHg early, and 32 mmHg at late follow-up). In the present HOCM patient, DDD pacing from a suitable site in the right ventricular apex caused a favorable reduction of LVOT gradient shortly after ICD implantation. In addition, there was a further significant reduction of LVOT gradient in DDD pacing and no recurrence of pulmonary edema over seven years. DDD pacing caused long-term reduction of the LVOT gradient and improvement of symptoms. Furthermore, the LVOT gradient meas-
ured this time in sinus rhythm was much lower than that recorded just after ICD implantation. There are few reports about LVOT gradient reduction measured in sinus rhythm at late follow-up.\(^5\) There are some discrepancies between the acute and chronic effects of DDD pacing. Reduction of the LVOT gradient decreases the pressure overload on the LV wall and causes ventricular remodelling in relation to asynchrony, bringing about a long-term effect. In the present case, however, regression of hypertrophy in the interventricular septum, which had occurred as a result of remodeling, was not observed after chronic DDD pacing. Fananapazir et al. reported that there was no correlation between the reduction in LVOT gradient and the change in LV wall dimensions.\(^5\) Therefore, regression of hypertrophy may be not only secondary to the reduction of LVOT gradient, but also a direct consequence of pacing.

**Mechanism of LVOT gradient reduction**

There are several anatomical and functional explanations for the development of LV outflow obstruction, including Venturi forces,\(^9\) septal bulge,\(^9\) elongation of the mitral leaflets,\(^9\) and anterior displacement of the papillary muscles.\(^10\) The mechanism by which DDD pacing may reduce the LVOT gradient is not elucidated sufficiently. Some investigators have suggested that pacing may influence myocardial perfusion\(^11\) and asynchronous ventricular septal activation,\(^4\) produce paradoxical movement of the septum\(^5,9\) or a negative inotropic effect,\(^12\) decrease mitral valve systolic anterior motion,\(^4,5\) or increase end-systolic volume.\(^12\) Recently, Hozumi et al. investigated the effects of DDD pacing on regional wall deformation, particularly of the ventricular septum.\(^13\) In patients with HOCM, DDD pacing led to myocardial lengthening, especially at the basal septum, as expressed in his paper by the increase in echocardiographic peak strain and SR after DDD pacing. These changes appeared to be related to the degree of LVOT gradient reduction.

**Isoproterenol administration**

Isoproterenol has a β-agonist property, which increases contractility and decreases afterload. This medical agent is useful in eliciting latent gradients in patients with hypertrophic cardiomyopathy. In the present patient at a cardiac catheterization study the LVOT gradient was no more than 10 mmHg in sinus rhythm. After administration of isoproterenol, however, the LVOT gradient was increased to 92 mmHg in sinus rhythm. Isoproterenol better simulates the hemodynamic effect of exercise, and so the effect of LVOT gradient reduction was insufficient during exercise in the present patient. It is thought that DDD pacing itself brings about LVOT gradient reduction during exercise.

**Location of pacing**

In the present HOCM patient, pacing using an additional ventricular pacing lead in addition to the defibrillation lead reduced the LVOT gradient to a greater extent, although both leads were located in the right ventricular apex. Matsumoto described a case in which the extent of LVOT gradient reduction differed significantly by a subtle difference of pacing site in the right ventricular apex.\(^14\) One presumed explanation for this is a change of paradoxical septal movement. However, the detailed mechanism is unknown, and further examinations by echocardiogram or myocardial scintigraphy are needed. In order to obtain a good outcome by DDD pacing, it is necessary to perform right ventriculography, determine the exact localization of the right ventricular apex, and insert the ventricular lead at the right ventricular apex with certainty. Considering the good result in our case, it may be better to optimize the pacing effect by determining the pacing site in a suitable place in the right ventricular apex.

**Study limitation**

We experienced a HOCM case in which DDD pacing from a suitable location in the right ventricular apex caused a marked early reduction in the LVOT gradient, and additionally, a further significant effect was obtained without ventricular pacing, also in sinus rhythm at late follow up for about seven years. However, we have not clarified the following study limitations. One possible limitation is that the longer-term effect of LVOT gradient reduction at more than seven years might not be steadily maintained, if ventricular pacing had been turned off and follow-up continued for a while. The other possible limitation is that prediction of a positive hemodynamic effect of DDD pacing has not been clearly established yet. To evaluate the limitations of our results, a further study with a large number of patients in a long-term randomized trial is needed in order to establish DDD pacemaker implantation as highly effective therapy for HOCM refractory to medical therapy.

**Summary**

Our HOCM case with an excellent outcome strongly suggests that DDD pacing from a suitable site in the right ventricular apex causes a marked early reduction in LVOT gradient, and at late follow
up continuous DDD pacing over seven years significantly decreased the gradient further also in sinus rhythm. We hope that our method described in this paper might become standard treatment for HOCM refractory to medical therapy.

References


