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Successful Induction of β-blocker Therapy for a Patient with Peripartum Cardiomyopathy Complicated with Significant Aortic Stenosis

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Summary. **A 35-year-old female with pre-existing significant aortic stenosis was admitted due to congestive heart failure commencing six months after her fourth delivery, and was diagnosed as peripartum cardiomyopathy. Because of severe contractile dysfunction, the aortic valve pressure gradient had decreased remarkably, indicating low-output, low-gradient aortic stenosis. In addition to the conventional therapies of heart failure, steroid therapy and intravenous immunoglobulin therapy were administered for coexisting myocarditis. While effective, the therapies were incomplete to relieve her symptoms and improve the low output state. For severe left ventricular systolic dysfunction, β-blocker therapy was initiated despite preexisting aortic stenosis. After the successful induction of β-blocker therapy, the patient's symptoms improved gradually. Her left ventricular systolic function has continued to improve with β-blocker therapy over two years of follow-up, and the aortic valve pressure gradient is reaching the level prior to the peripartum cardiomyopathy. β-blocker therapy may constitute one option among the therapeutic strategies for intractable heart failure due to cardiomyopathy even if complicated with significant aortic stenosis.**

Key words—aortic stenosis, β-blocker, left ventricular dysfunction, peripartum cardiomyopathy, heart failure.

INTRODUCTION

β-blockers have recently come to be regarded as one of the most effective drugs for controlling chronic heart failure due to severe left ventricular dysfunction[1,2]. On the other hand, β-blockers are also considered to be contraindicated in patients with severe aortic stenosis because of the concern that they may cause life-threatening low cardiac output or low blood pressure[3]. Therefore, the induction of a β-blocker for patients with severe left ventricular dysfunction complicated with aortic stenosis has rarely been reported. Among patients with low-output aortic stenosis, those who have primary myocardial disease have a poor prognosis even with aortic valve replacement[4], and no effective therapy has been reported. For such cases, once the aortic valve pressure gradient has declined with the progression of the primary myocardial disease, β-blocker therapy may have to be taken into consideration. We have present a case of critical peripartum cardiomyopathy with preexisting significant aortic stenosis which was successfully treated with a β-blocker.

CASE REPORT

A 35-year-old woman with aortic stenosis was admitted to our hospital due to the peripartum development of cardiomyopathy. In 1989, when she was 23 years old, a percutaneous transluminal mitral comissurotomy was performed for significant mitral

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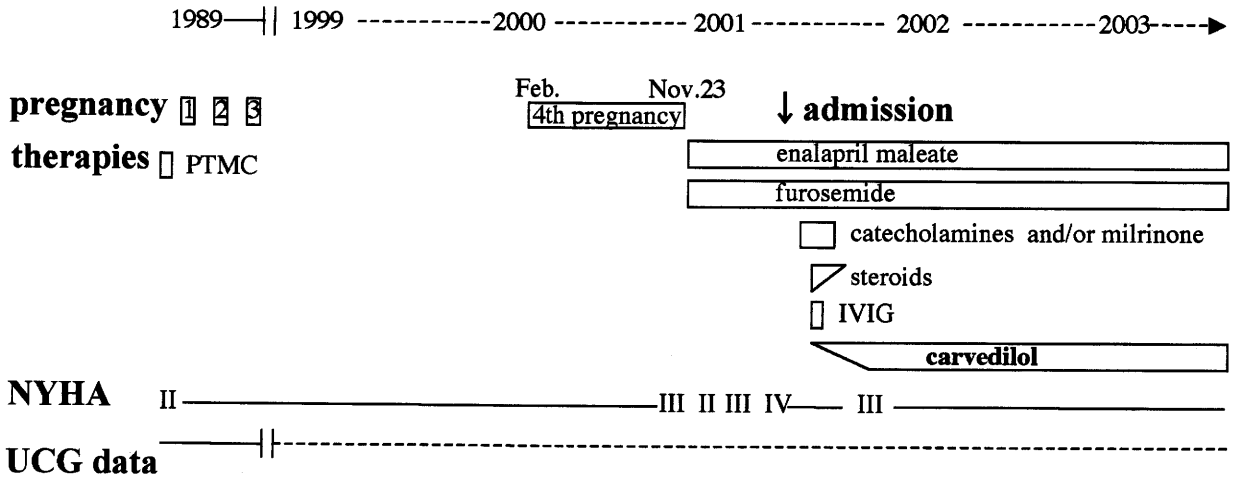
Abbreviations—CTR, cardiothoracic ratio.



	1989 post PTMC	1999 Feb.2	2000 Mar.6	Aug.10	Dec.7	2001 May2	June3	June18	2002 Sept.1	2003 May 1
LVEDD(cm)	5.3	5.4	5.7	6.6	6.9	7.7	7.6	7.5	7.7	7.7
LVESD(cm)	3.9	4.0	3.9	4.8	5.8	6.8	7.1	6.7	6.8	6.1
FS	0.26	0.26	0.32	0.27	0.16	0.12	0.07	0.10	0.12	0.20
EF	0.51	0.51	0.59	0.52	0.33	0.25	0.14	0.21	024	040
IVS(cm)	1.0	0.9	0.7	0.9	1.0	1.0	0.8	0.9	0.8	0.9
PW(cm)	0.9	0.8	0.9	0.7	0.9	0.7	0.9	0.9	0.8	0.8
MR	(–)	1-2°	1°	2°	2°	2-3°	3°	2-3°	1°	1°
MVA(PHT)(cm^2)	2.2	1.1	1.2	1.3	1.5	1.3	1.5	N.D.	N.D	1.6
AR	2°	3°	2-3°	3°	3°	3°	3°	2-3°	3°	3°
AV-PG(mmHg)	N.D.	N.D.	67-69	N.D.	N.D.	N.D.	22	N.D.	48	59

Fig. 1. Clinical course and changes in echocardiographic parameters. During the patient's fourth pregnancy, her left ventricular cavity started to dilate, and deterioration of the systolic function was detected just after delivery. On admission, AV-PG had decreased remarkably with further deterioration of the systolic function. With long-term β-blocker therapy, FS, EF, and AV-PG have been gradually increasing. NYHA, New Yok Heart Association functional class; LVEDD, left ventricular end systolic dimension; LVESD, left ventricular end diastolic dimension; FS, fractional shortening; EF, ejection fraction; IVS, intraventricular septum; PW, posterior wall; MR, mitral regurgitation; MVA, mitral valve area; PHT, pressure half time; AV-PG, aortic valve pressure gradient; PTMC, percutaneous transluminal mitral comissurotomy; N.D., not done.

stenosis probably caused by rheumatic fever. The procedure was successful without mitral regurgitation or complications. At that time, no aortic stenosis was detected, although aortic regurgitation was moderate and her left ventricular ejection fraction had already been reduced to 51% (Fig. 1). Later, she bore three children via normal vaginal deliveries, and there was no progress in the left ventricular systolic dysfunction until her fourth pregnancy in February, 2000. In March, her aortic valve pressure gradient was measured by echocardiography for the first time, and it was 67–68 mmHg with almost normal left ventricular systolic function. No left ventricular hypertrophy had ever been detected by echocardiography. The patient gave birth via a normal vaginal delivery on November 23 without cardiac symptoms, despite a dilatation of the left ventricle detected by an echocardiography in August (Fig. 1). Ten days later, coughs with bloody sputa appeared. Her chest X-ray showed cardiomegaly (cardiothoracic ratio (CTR)=63%) and pulmonary congestion. An echocardiography revealed left ventricular dilatation and a declined ejection fraction (Fig. 1). Enalapril maleate 2.5 mg/day and furosemide 20 mg/day were prescribed. The patient's symptoms and pulmonary congestion improved and CTR was reduced to 55% by January 15, 2001. However, on May 2, an echocardiography revealed further dilatation of her left ventricular cavity and a deterioration of the left ventricular systolic function even while continuing the same regimen (Fig. 1). Coughs with bloody sputa reappeared on May 24, and the patient was admitted

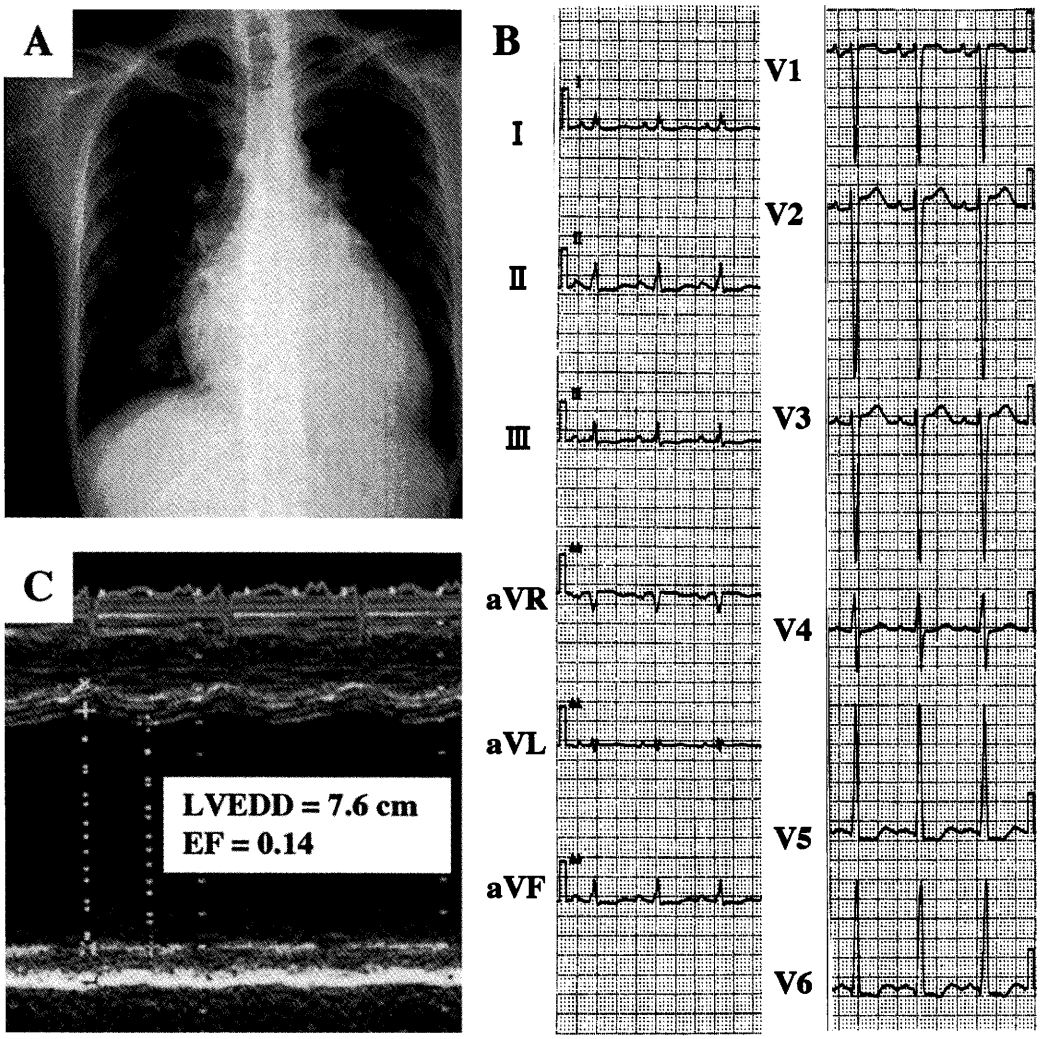


Fig. 2. The electrocardiogram (**A**), chest X-ray (**B**), and M-mode echocardiography (**C**) on admission. LVEDD, left ventricular end diastolic dimension; EF, ejection fraction.

to our hospital on May 28.

On physical examination, her height and weight were 164 cm and 46.5 kg. Her body temperature was 36.8°C. Her pulse rate was 98 beats/min, and blood pressure was 86/50 mmHg. On auscultation, coarse crackles on her lower lung fields, systolic ejection murmur, and early diastolic murmur at the upper right sternal border, opening snap, and diastolic rumble at apex were audible. CTR increased up to 65% (Fig. 2A). The electrocardiogram showed high voltage in leads $V_{5,6}$, S-T segment depression and flat or biphasic T waves in leads, II, III, aV_F, $V_{5,6}$ (Fig. 2B). Echocardiograms showed severe left ventricular systolic dysfunction (EF=11-14%) and a decreased aortic valve pressure gradient (22 mmHg) compared with the prior examination (67-69 mmHg) (Fig. 1 and 2C). Laboratory tests showed mild inflammation (CRP=1.2 mg/dl) and myocardial damage (myosin light chain 3.9 ng/dl, troponin T 0.47 ng/ml).

Pulmonary congestion was controlled with diuretics, but low output syndrome with dyspnea, overwhelming weakness, and cold sweating could not be controlled even with catecholamines (dobutamine, 6 μg/kg/min, and dopamine, 3 μg/kg/min) and a phosphodiesterase inhibitor (milrinone, 0.4 μg/kg/min). Further increments of inotropic agents were not attempted because non-sustained ventricular tachycardia appeared. Methylprednisolone pulse therapy was then employed against probable myocarditis; her symptoms improved for several days but then deteriorated again. Cardiac catheterization performed on June 13 showed low-gradient aortic

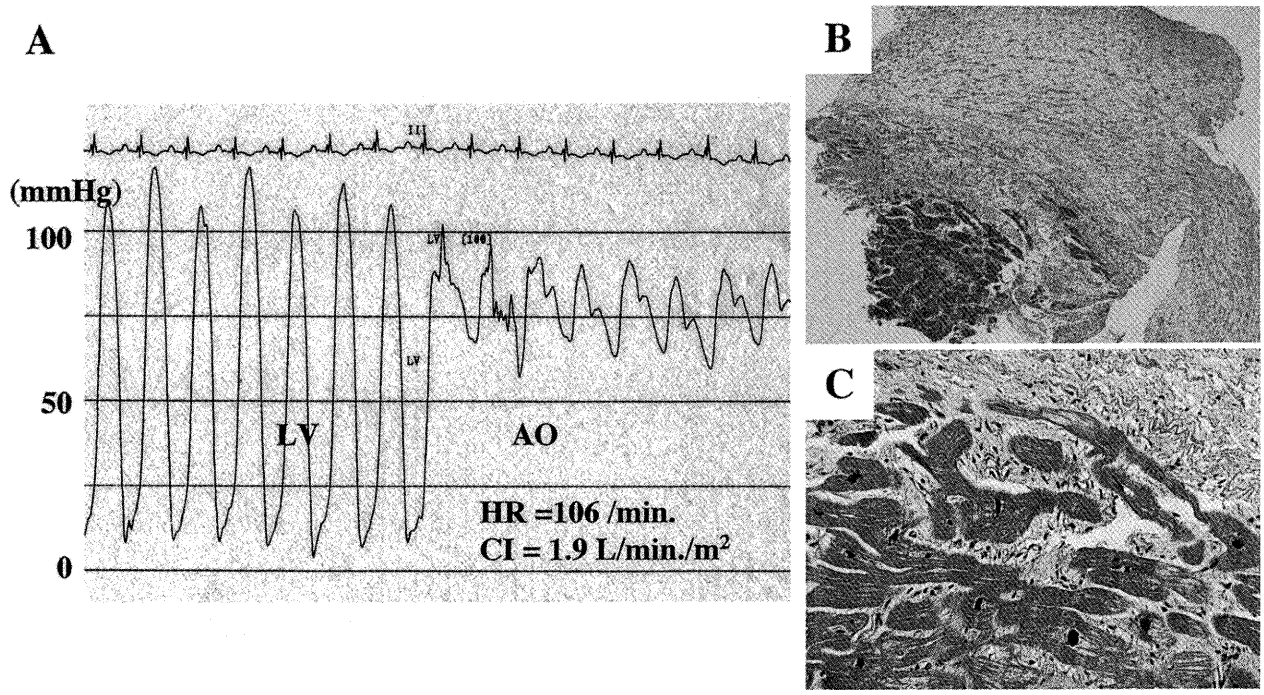


Fig. 3. Pressure recording of the left ventricle and aorta in the acute phase (**A**) revealed low-gradient aortic stenosis. Mechanical alternans was also detected in the left ventricular pressure. Histology of the endomyocardial biopsy (hematoxylin -eosin; **B**, ×100; **C**, ×400) showed endocardial thickening and cellular infiltration. Endocardial fibrosis was severe, and fibrous tissue surrounding myocytes was also detected. LV, left ventricle; AD, aorta; HR, heart rate; CI, cardiac index.

Table 1. Changes in hemodynamic parameters

	HR	RA	RV	PA	PCWP	LV	CO	CI	MVA	AVA
	(/min.)	(mmHg)	(mmHg)	(mmHg)	(mmHg)	(mmHg)	(L/min)	(L/min/m²)	(cm²)	(cm²)
2001.6.13.	106	(2)	34/EDP7	32/18 (23)	(19)	114/EDP18	2.7	1.9	1.4	N.D.
2002.7.14.	72	(1)	22/EDP2	22/10 (14)	(9)	116/EDP13	3.3	2.2	2.5	0.9

HR, heart rate; RA, right atrium; RV, right ventricle; EDP, end-diastolic pressure; PA, pulmonary artery; PCWP, pulmonay capillary wedge pressure; LV, left ventricle; AO, aorta; CO, cardiac output; CI, cardiac index; MVA, mitral valve area; AVA, aortic valve area; N.D., not done. The number in parentheses is the mean value.

stenosis (about 25 mmHg from peak to peak, Fig. 3A) with a low cardiac index (1.9 l/min./m²) (Table 1). An endomyocardial biopsy revealed endocardial thickening and a mild infiltration of lymphocytes and plasma cells (Fig. 3B and C). Methylprednisolone pulse therapy was employed again with intravenous immunoglobulin therapy followed by oral prednisolone. Additionally, carvedilol was started at a dose of 1 mg/day, and the dose was gradually increased. Her symptoms, sinus tachycardia (90-120/min), and left ventricular systolic dysfunction remained unchanged for about four weeks until the dose of carvedilol was increased up to 10 mg/day. Afterwards, the low output syndrome improved gradually with a decrease in heart rate. Finally, the dose of carvedilol was increased up to 20 mg/day without any exacerbation of heart failure, and the patient was discharged. One year later, she was admitted to our hospital for reevaluation of her cardiac status. Her hemodynamic parameters had improved except for a decrease in systemic blood pressure and an increase in the aortic valve pressure gradient (Table 1, Fig. 1 and 4A). Two years after the induction of carvedilol, the patient has remained clinically stable, her ventricular systolic function has been improving, and the aortic valve pressure gradient is gradually reaching the level prior

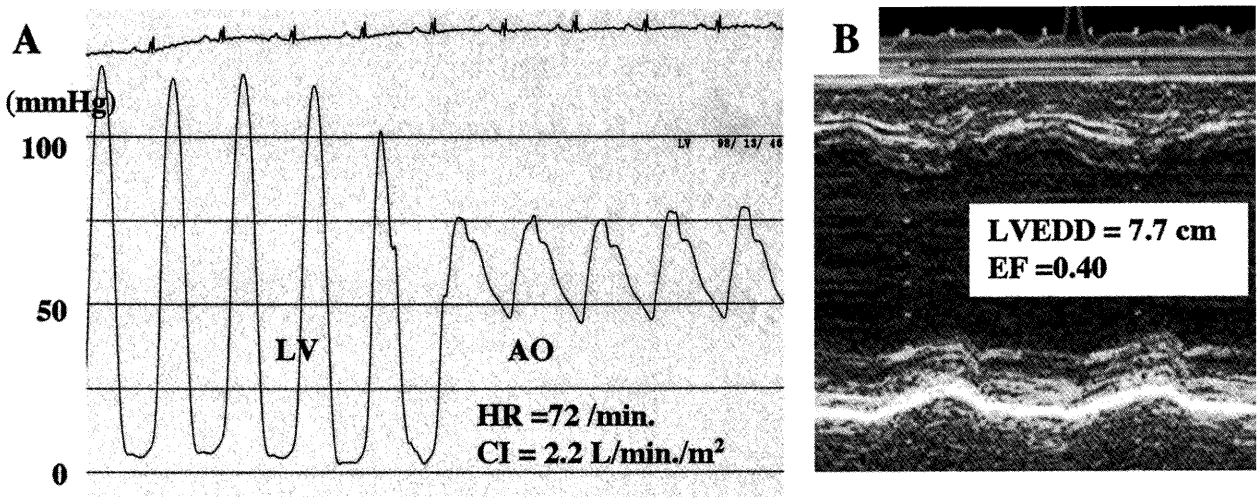


Fig. 4. Pressure recording of the left ventricle and aorta one year afler admission (**A**) shows decreased systemic blood pressure and an increased aortic valve pressure gradient. Mechanical alternans has almost vanished. M-mode echocardiography two years after admission (**B**) indicates that her left ventricular systolic function is improving. LV, left ventricle; AO, aorta; HR, heart rate; CI, cardiac index; LVEDD, left ventricular end diastolic dimension; EF, ejection fraction.

to the peripartum cardiomyopathy (Fig. 1 and 4B).

DISCUSSION

Hemodynamic responses to inotropic stimulation have recently been reported to be useful[4,5] in determining strategies for the treatment of patients with low-output, low-gradient aortic stenosis. Among these, those whose stroke volume does not increase by dobutamine stimulation may have a primary contractile dysfunction, and their prognosis is considered to be poor even with aortic valve replacement[4]. In the patient under discussion, clinical symptoms of low cardiac output did not improve with inotropic agents, and peripartum cardiomyopathy was the cause of the left ventricular dysfunction. Furthermore, any improvement of left ventricular function after aortic valve replacement was unlikely with severe endocardial fibrosis and a dilated left ventricular cavity[6,7]. We therefore focused on therapies for the primary contractile dysfunction.

The prognosis of patients with peripartum cardiomyopathy depends on the normalization of the left ventricular size and function within 6 months after delivery[8]. Approximately half of the patients have persistent left ventricular dysfunction and a poor prognosis: 85% mortality over 5 years in one study[9], with no effective therapy reported.

Peripartum cardiomyopathy is often complicated with myocarditis[10,11]. Steroids and intravenous immunoglobulin therapy can be effective for peripartum cardiomyopathy and myocarditis[10,12]. These therapies seemed effective at first for this patient to terminate the progressive exacerbation of the left ventricular dysfunction, but the (left ventricular) dysfunction remained severe and symptoms did not improve, even after cessation of the inflammation. Therefore, therapies to control chronic heart failure were needed.

β-blockers are one of the most effective drugs to improve the mortality and morbidity of patients with severe left ventricular dysfunction, at least in nonvalvular heart failure.[12,13] In this patient, if the cause of the left ventricular dysfunction was secondary to aortic stenosis, β-blockers would not have been used. However, the contractile dysfunction was caused primarily by peripartum cardimyopathy, and the contribution of aortic stenosis to heart failure seemed much less than that of the primary contractile dysfunction. In such cases, no guidelines for the induction of β-blockers are currently available. Among the available β-blockers, we prescribed carvedilol because it could be effective both for severe cardiac failure[1,13] and for peripartum cardiomyopathy[14].

The mechanisms by which β-blockers improve heart failure have not been fully elucidated. Possible mechanisms include myocardial protective actions against catecholamine toxicity, antioxidant effects, the prevention of myocardial hypertrophy and ventricular remodeling, antiapototic effects, and

beneficial metabolic effects[15]. From these points of view, β-blockers can be effective even for patients complicated with aortic stenosis. In an animal model of supravalvular aortic banding, carvedilol prevented left ventricular dilatation, hypertrophy, and fibrosis[16]. Actually, in this case, no adverse effects were observed during the period of induction, and with long-term β-blocker therapy, the left ventricular function has been improving. Although it is unknown whether or not the improvement especially depended on carvedilol such delayed effects are characteristic of β-blocker therapy[17].

In conclusion, β-blockers can be effective for the treatment of patients with a left ventricular dysfunction complicated with aortic stenosis, at least when the aortic valve pressure gradient is low and the cause of left ventricular dysfunction is primary myocardial disease.

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