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Xamoterol in patients with dilated cardiomyopathy: An increase in β-receptors in lymphocytes

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Summary

Xamoterol, a partial-β_1 agonist, was administered orally (100 mg, twice daily) to healthy volunteers (n=8) and to patients with heart failure (n=8) for one week. The density (Bmax) and affinity (Kd) of lymphocyte β-receptors were lower in the patients with heart failure than in the healthy volunteers (Bmax=931±214 vs 1466±373 sites/cell, and Kd=0.60±0.11 vs 1.07±0.14 nM). During treatment with xamoterol, Bmax (7169±3768 and 7749±3807 sites/cell) and Kd (6.01±3.84 and 9.06±4.66 nM) increased strikingly ($p<0.01$) in both groups.

For 12 months, xamoterol (100 mg bd) was given in the same manner to 10 patients with dilated cardiomyopathy. The long-term effects after three and 12 months were assessed. Xamoterol reduced the cardiothoracic ratio from 57±6% to 55±5% after three months and 54±5% after 12 months of treatment (both $p<0.05$), and increased exercise tolerance from 5±2 min to 7±2 min and to 7±2 min ($p<0.01$, $p<0.05$). Echocardiographic fractional shortening increased from 13±6% to 20±8% ($p<0.01$) and to 20±10% ($p<0.05$). Pulmonary wedge pressure during exercise at the same work load decreased from 40±12 mmHg to 25±9 mmHg ($p<0.01$) in three months; whereas pulmonary wedge pressures during exercise or at rest in 12 months were unchanged. Exercise heart rate decreased from 118±9 beats/min to 106±6 beats/min in three months ($p<0.01$), but was unchanged in 12 months. Bmax and Kd of the β-receptors increased from 1024±413 sites/cell and 0.67±0.27 nM to 1976 ±497 sites/cell and 1.60±0.42 nM (both $p<0.01$), respectively, in three months, and 1584±650 sites/cell (NS) and 1.21±0.54 nM ($p<0.05$), respectively, in 12 months.

It is concluded that xamoterol improves exercise tolerance, hemodynamics and resolves subjective symptoms for certain patients with dilated cardiomyopathy by its actions as a β-agonist and β-antagonist during longterm treatment.

Key words

Xamoterol | β_1-partial agonist | β-receptor | Dilated cardiomyopathy | Heart failure

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Introduction

Recently, quantitative and qualitative changes in receptors have been studied since radioligand binding assay and purification of receptor proteins have advanced[1,2]. There is evidence that changes in β-receptors in the myocardial membrane and in lymphocytes in patient with heart failure are closely related to the pathophysiology and treatment of this condition[3].

Dilated cardiomyopathy (DCM) is a disease of unknown etiology which is characterized by left ventricular dilatation and reduced contractility. The prognosis is variable but is generally poor[4,5]. Present therapy is unsatisfactory as it is only palliative, and not curative[6,7].

Pathologically-increased levels of norepinephrine in patients with DCM may damage the myocardium and cause progressive congestive heart failure[8]. Therefore, therapy with β-antagonists has been attempted to modify the progress of the disease[9,10].

Xamoterol (ICI 118,587 " Corwin ") is a partial agonist which acts on β-receptors, and it has 43% of the maximum activity of isoprenaline[11]. When sympathetic tone is relatively high, xamoterol acts as an antagonist. Because of its pharmacological properties, it appears that xamoterol would stabilize the response of the heart to sympathetic stimulation. Thus, it is expected that xamoterol will be clinically beneficial in patients with DCM, in whom excessive plasma catecholamines have produced β-receptor downward-regulation[12].

In the present study, xamoterol was given to healthy volunteers and to patients with heart failure, and the β-receptors in the lymphocytes were assayed before and after treatment using ^{125}I-iodocyanopindolol (ICYP) radioligand binding assay. We also investigated the long-term effects of xamoterol in patients with DCM, based on changes in hemodynamics, exercise tolerance and β-receptors in lymphocytes.

Subjects and Methods

1. β-receptors in lymphocytes following treatment with xamoterol.

1. Control group: For seven days, xamoterol (100 mg twice a day) was given orally to eight healthy male volunteers aged 18 to 23 years, whose mean age was 20 years. Blood pressure, heart rate, β-receptors in lymphocytes and fractional shortening (FS) by M-mode echocardiogram were recorded before treatment, and on days two, five and seven during treatment, and again two and five days after withdrawal of the drug.

2. Heart failure group: Xamoterol in the same doses was given orally for seven days to eight patients with chronic heart failure of the class II or III according to the criteria of the New York Heart Association (NYHA), which had persisted one month or more. Their ages ranged from 46 to 65 years, with a mean ages of 58 years. Five were men and three, women. DCM was detected in six and valvular heart disease, in two. All subjects were tested before and after treatment, as were the healthy volunteers. The mean cardiothoracic ratio (CTR) was 68±8%. Digitalis, diuretics and vasodilators were also administered during the study, without any changes in regimens. No patient received β-agonists or β-antagonists concurrently.

2. The long-term effects of xamoterol in patients with DCM

Ten patients with DCM, eight men and two women, whose mean age was 59 years, were admitted to this study. DCM was confirmed by left ventriculography, coronary angiography and echocardiography, according to the criteria of WHO/ISFC[13]. All patients had symptoms of moderate heart failure (NYHA class II-III) and six were in sinus rhythm and four in atrial fibrillation. Patients who had received β-agonists or antagonists were excluded from this study. Digitalis, diuretics, vasodilators, antiarrhythmics and anticoagulants were continued and the doses were kept constant throughout the study. This study was begun when the patients had been in stable clinical condition at least one

month after being initially diagnosed.

Xamoterol (100 mg twice a day) was administered to the patients for one year. The following measurements were made before, and three months and 12 months after administration.

3. Special methods of study

1. Chest radiography: Cardiothoracic ratio (CTR) was calculated from the chest radiograph.

2. Exercise tolerance: Exercise tolerance was determined by multistage bicycle ergometer exercise in the supine position. The initial load was 25 watts, followed by an increase of 25 watts every three min. The exercise test was discontinued when dyspnea, fatigue or chest pain occurred or if hypotension or a severe arrhythmia appeared.

3. Echocardiography: Echocardiograms were recorded using a phased array electronic sector scanner with a transducer frequency of 2.4 MHz (Model SSH-11A. Toshiba Co). Fractional shortening (FS) and the left ventricular ejection fraction (EF) were calculated from left ventricular end-diastolic (LVDd) and end-systolic (LVDs) dimensions using the Teicholz's formula[14].

4. Right heart catheterization: In all of the 10 patients having long-term treatment, right heart catheterization was performed before and after xamoterol administration. The mean pulmonary arterial pressure (mPA) and pulmonary wedge pressure (PAW) were measured by means of a 7.5F Swan-Ganz catheter introduced percutaneously via the right femoral vein into the pulmonary artery. Measurement of cardiac output was performed in triplicate by the thermodilution method (American Edwards Lab 9520A Edwards Co) and was used to calculate the cardiac index (CI) and stroke volume index (SI). Resting heart rate and systolic blood pressure were measured.

5. Hemodynamics at submaximum exercise: After the introduction of the Swan-Ganz catheter, hemodynamic variables were measured at the submaximum exercise load which was previously determined by a preliminary multistage supine bicycle exercise test. After three and 12 months of the treatment with xamoterol, the hemodynamic variables were measured at the same workload as before the xamoterol administration. If the exercise tolerance after administration was lower than before the drug was given, it was measured at the same exercise level.

6. Isolation of lymphocytes and binding assay: In all of the control group and heart failure group, and in eight of the 10 patients with long-term treatment, β-receptors in lymphocytes were identified by radioligand binding assay. Heparinized 10 m*l* blood samples were drawn, laid on Ficoll Conray according to the Boyum's method, and centrifuged at 1,500 rpm for 30 min to isolate the lymphocytes. The latter were washed twice with PBS at 1,000 rpm for 10 min, and suspended in a mixture of 60 mM Tris-HCl and 20 mM $MgCl_2$ at PH 7.4. The lymphocytes were incubated with ICYP at 23°C for 45 min and then filtered through a glass fiber filter (GF/C, Whatman). Radioligand bound to lymphocytes was assayed by an Autowell gamma counter (ARC-251, Aloka). The lymphocytes were incubated with and without 10 μM 1-propranolol, and the radioligand binding suppressed by propranolol was defined as the binding specific to β-receptors. The radioligand was used at six to 12 concentrations, and the results were analyzed using the Scatchard's test. Then Bmax and Kd of the β-receptors were calculated[15]. Proteins were assayed by the Lowry's method, and the number of β-receptors per lymphocyte was calculated by the method of Galant et al[16,17].

Statistical analysis

All data were expressed as means±1 standard deviation and differences in means were assessed by the Student's t-test. Values of $p<0.05$ were considered significant.

Results

1. Blood pressure, FS and β-receptors in lymphocytes following treatment with xamoterol in the control and in the heart failure groups

1. Blood pressure, heart rate and FS (**Table 1**):

Table 1. Effects of xamoterol on hemodynamics and β-receptors in the control (healthy volunteers) **and the heart failure groups**

	Before	Xamoterol			Withdrawal	
		2	5	7 (days)	2	5 (days)
(A) Healthy volunteers						
Heart rate (beats/min)	78±15	81±7	75±13	86±13	78±11	73±11
Systolic BP (mmHg)	118±17	127±17*	133±19*	126±16*	122±16	120±15
Fractional shortening (%)	35±3	38±4*	39±3*	39±3*	36±4	35±3
Bmax (sites/cell)	1466±373	7169±3768**	4946±2500**	5130±2889**	1998±214*	1420±383
Kd (nM)	1.07±0.14	6.01±3.84**	3.55±2.30**	2.61±1.15**	0.99±0.21	1.01±0.16
(B) Heart failure						
Heart rate (beats/min)	70±9	72±11	75±7	71±8	74±8	76±8
Systolic BP (mmHg)	110±13	115±11	127±16*	121±11*	117±5	116±11
Fractional shortening (%)	19±7	19±7	20±8	20±9	20±9	19±8
Bmax (sites/cell)	931±214	7749±3807**	4293±2160**	4125±1928**	1696±435**	1385±457**
Kd (nM)	0.60±0.11	9.06±4.66**	2.73±2.16**	2.56±1.67**	1.63±0.70**	0.61±0.14

Values are means±1SD.
BP=blood pressure; Bmax and Kd=density and affinity of the β-receptors.
* $p<0.05$ and ** $p<0.01$ when compared with values before xamoterol administration.

Blood pressure rose slightly during the treatment in both the healthy volunteers and the patients in heart failure, but heart rate was unaffected. FS increased slightly during the treatment in the healthy volunteers, but it returned to the pretreatment level after withdrawal of xamotorol. FS was much lower in the patients in heart failure than in the healthy volunteers (35±3% vs 19±7%, $p<0.01$) and was not affected by the drug.

2. β-receptors in lymphocytes (**Table 1, Fig. 1**):

In the control group, both Bmax (1466±373 vs 7169±3768 sites/cell, $p<0.01$) and Kd (1.07±0.14 vs 6.01±3.84 nM, $p<0.01$) increased strikingly from the pretreatment levels on day two of the treatment. During the treatment, both Bmax and Kd remained elevated, then returned to pre-treatment levels after withdrawal of xamoterol.

In the heart failure group, pretreatment Bmax (931±214 sites/cell, $p<0.05$) and Kd (0.60±0.11 nM, $p<0.05$) were lower than in healthy volunteers. On day two of treatment, Bmax (7749±3807 sites/cell, $p<0.01$) and Kd (9.06±4.66 nM, $p<0.01$) increased strikingly, and during the treatment both these factors remained higher than the pretreatment levels. Both Bmax and Kd decreased after withdrawal of xamaterol. Kd returned to the pretreatment levels on day five after withdrawall of xamaterol, while Bmax was still higher than the pretreatment level (1385±457 sites/cell, $p<0.05$).

2. Long-term effect of xamoterol in patients with DCM

All 10 patients received xamoterol for one year, and no adverse reactions were observed.

1. CTR, exercise tolerance and echocardiographic measurements (**Table 2, Fig. 2**):

CTR was reduced significantly from 57±6% before xamoterol administration to 55±5% after three months and 54±5% after 12 months

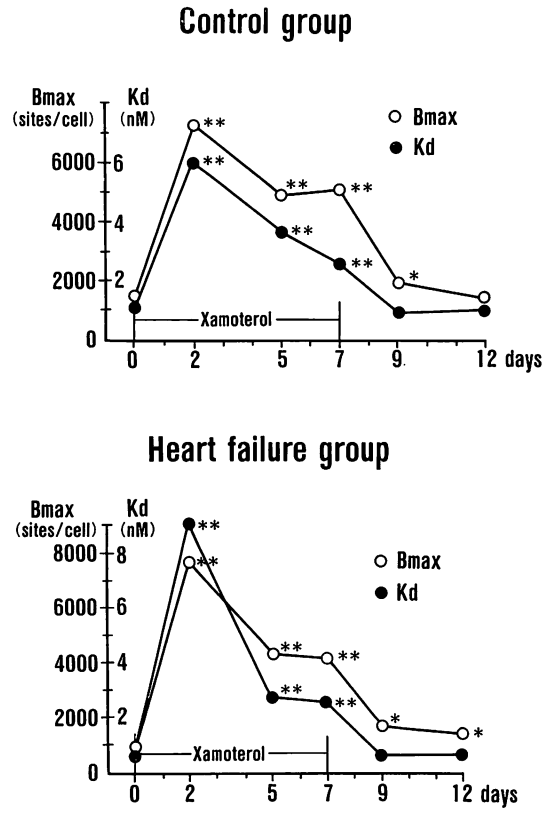

Fig. 1. Acute effects of xamoterol administration on the density (Bmax=sites/cell) **and affinity** (Kd=nM) **of the lymphocyte β-receptors in the control and the heart failure groups.**

Each point is the mean of values of all subjects.
* $p<0.05$ and ** $p<0.01$ vs pretreatment days.

treatment (both, $p<0.05$). Mean exercise duration increased from 5±2 to 7±2 min and 7±2 min ($p<0.01$, $p<0.05$). An increase in exercise tolerance was observed in all patients after three months. After 12 months, a decrease in exercise tolerance was observed in one patient. LVDd in echocardiography decreased from 6.3±0.9 cm to 5.9±0.9 and 5.9±1.0 cm ($p<0.01$ and $p<0.05$), respectively. LVDs decreased from 5.4±1.0 cm to 4.7±1.1 cm and 4.8±1.3 cm ($p<0.01$ and $p<0.05$), respectively. EF increased from 30±13% to 39±13% and 38±18% ($p<0.01$ and $p<0.05$), respectively. FS increased significantly from 13±6% to 20±8% and 20±10% ($p<0.01$ and $p<0.05$), respectively.

Table 2. Long-term effect of xamoterol on the cardiothoracic ratio, exercise tolerance and echocardiographic variables

	Before	3 months	12 months
CTR (%)	57±6	55±5	54±5
Exercise tolerance (min)	5±2	7±2**	7±2*
LVDd (cm)	6.3±0.9	5.9±0.9**	5.9±1.0*
LVDs (cm)	5.4±1.0	4.7±1.1**	4.8±1.3*
EF (%)	30±13	39±14**	38±18*
FS (%)	13±6	20±8**	20±10*

CTR=cardiothoracic ratio; LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; EF=ejection fraction; FS=fractional shortening.

Values are mean±1SD.

* $p<0.05$ and ** $p<0.01$ vs before.

2. Resting hemodynamic variables (Table 3 and Figure 3).

The only variable showing a significant change was PAW, which decreased from 16±3 mmHg to 11±4 mmHg after three months treatment ($p<0.05$). No change occurred in mean resting hemodynamic variables after 12 months treatment.

3. Exercise hemodynamic variables (**Table 3, Fig. 3**).

Exercise heart rate decreased significantly from 118±9 beats/min to 106±6 beats/min after three months treatment ($p<0.01$), but did not change after 12 months treatment (109±18 beats/min). PAW during exercise decreased from 40±12 mmHg to 25±9 mmHg and 32±16 mmHg ($p<0.01$ and NS), respectively. Other variables (CI, SI etc) did not change after three months and 12 months treatments.

4. β-receptor (**Table 4, Fig. 4**).

Pretreatment Bmax (1024±413 sites/cell) and Kd (0.67±0.27 nM) were lower in the patients than in the healthy volunteers (Bmax=1466±373 sites/cell, Kd=1.07±0.14 nM). After three and 12 months' treatment, Bmax (1976±497, $p<0.01$ and 1584±650 sites/cell, NS) and Kd (1.60±0.42, $p<0.01$ and 1.21±0.54 nM, $p<$

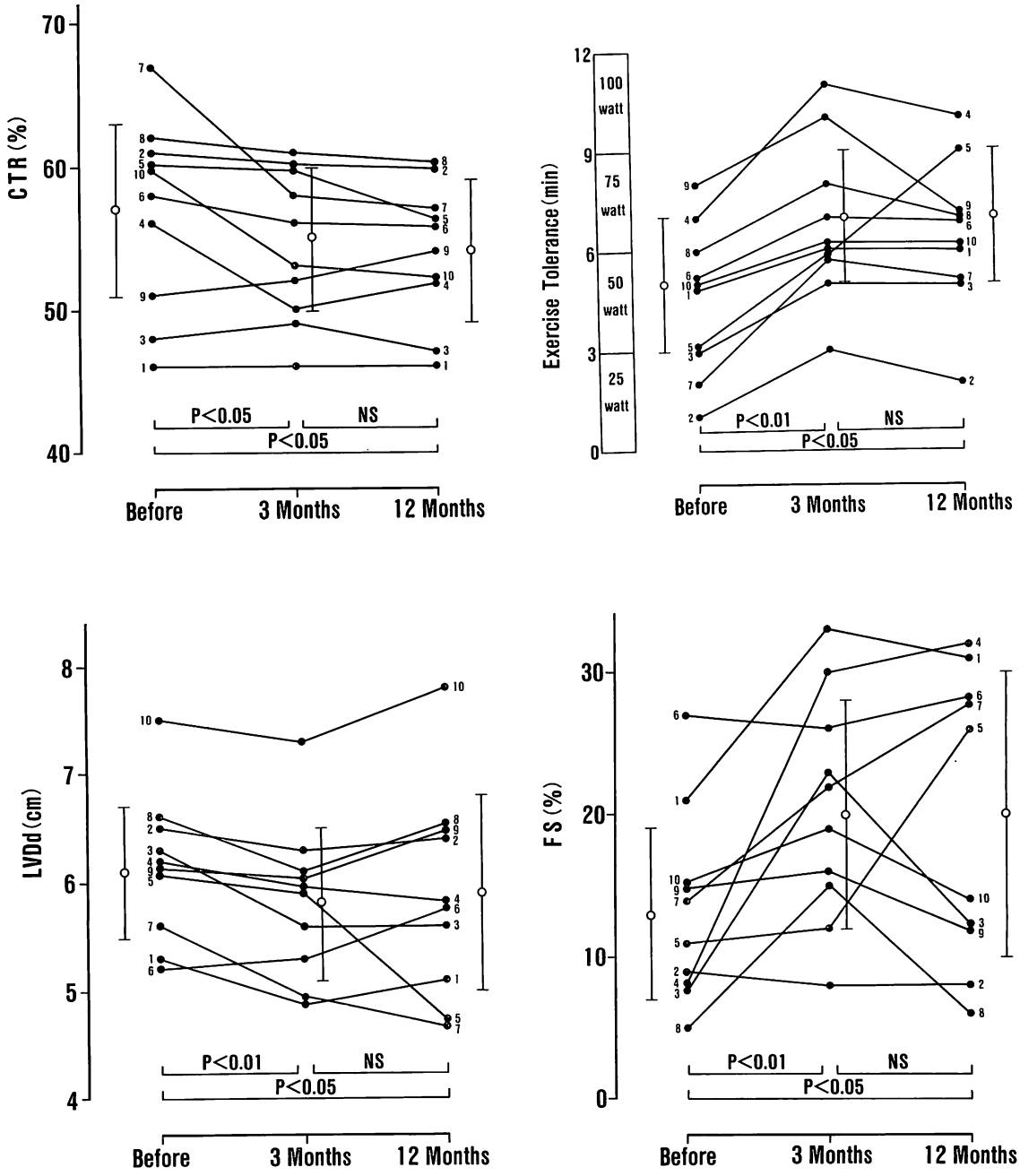

Fig. 2. Long-term effect of xamoterol on the cardiothoracic ratio (CTR), **exercise tolerance, left ventricular end-diastolic dimension** (LVDd) **and fractional shortening** (FS).
Numbers are patients' numbers.

Table 3. Long-term effect of xamoterol on resting and exercise hemodynamic variables

	Before		3 months		12 months	
	Resting	Exercise	Resting	Exercise	Resting	Exercise
Heart rate (beats/min)	65±12	118±9	68±12	106±6**	70±15	109±18
BP (systol/diast mmHg)	129±21	154±27	127±16	156±19	134±19	157±20
	70±12	82±15	71±11	88±12	80±7*	94±10
CI (L/min/m²)	2.41±0.48	4.74±1.14	2.58±0.36	4.78±0.84	2.55±0.39	4.54±1.11
SI (ml/m²)	38±10	39±9	38±6	43±19	37±9	42±10
mPA (mmHg)	22±3	49±14	20±5	40±13	22±7	45±17
PAW (mmHg)	16±3	40±12	11±4*	25±9**	16±8	32±16

BP=blood pressure; CI=cardiac index; SI=stroke index; mPA=mean pulmonary arterial pressure; PAW=pulmonary wedge pressure.

Mean±1SD. * $p<0.05$ and ** $p<0.01$ vs before.

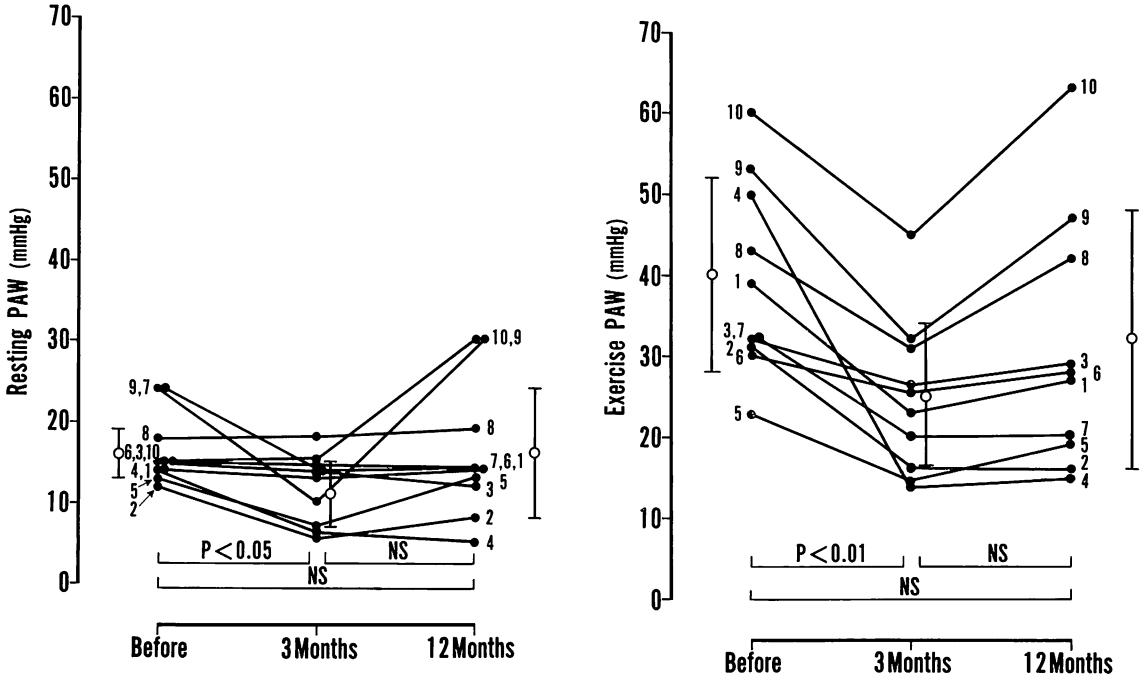

Fig. 3. Long-term effect of xamoterol on resting and exercise pulmonary wedge pressure (PAW).

0.05) increased. In three patients with high PAW, the β-receptor density and affinity returned to the pretreatment levels after 12 months treatment (Nos. 8, 9, 10). The density and affinity remained higher than the pretreatment levels in patients with low initial PAWs.

Table 4. Long-term effect of xamoterol on the levels of norepinephrine and β-receptor in lymphocytes and normal values in the controls

	Before	3 months	12 months	Healthy volunteers
Norepinephrine (ng/m*l*)	0.56±0.32	0.42±0.13	0.45±0.24	0.23±0.08
Bmax (sites/cell)	1024±413	1976±497**	1584±650	1466±373
Kd (nM)	0.67±0.27	1.60±0.42**	1.21±0.54*	1.07±0.14

Bmax=density of β-receptor; Kd=affinity of β-receptor.
mean±1SD. * $p<0.05$ and ** $p<0.01$ vs before.

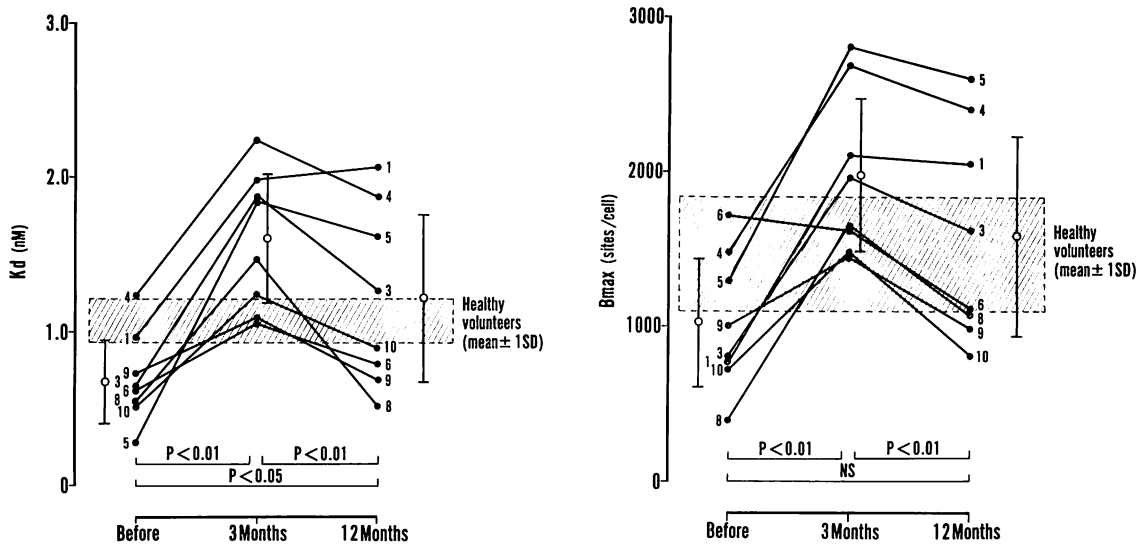

Fig. 4. Long-term effect of xamoterol on the density (Bmax) **and affinity** (Kd) **of lymphocyte β-receptors.**

Discussion

Digitalis, diuretics and vasodilators are the mainstay of treatment of cardiac failure with DCM. The use of new cardiotonics such as amrinone, milrinone and denopamine has recently been proposed. However, these drugs generally produce acute improvement, but there is no definite evidence of long-term response or improved prognosis. They may even worsen the prognosis, because the limited energy supply is consumed and arrhythmias may be provoked[18,19].

β-adrenergic full agonists are effective promptly in improving heart failure, but they lose their efficacy in long-term therapy because of decreases in density of myocardial β-adrenergic receptors, i.e., down-regulation[20]. Therefore, cardiotonics such as DBcAMP which do not increase cAMP through β-receptors have been clinically investigated, but their longterm efficacy has been disappointing[21].

Interestingly, β-blockers are effective in some patients with DCM who do not respond to conventional therapy for cardiac failure[9,10,22,23]. The efficacy of β-blockers may be explained by improved diastolic performance of the myocardium, protection of the myocardium from increased catecholamine levels and restoration of β-adrenoceptor sensitivity for catecholamines.

In general, however, β-blockers are likely to aggravate heart failure and are used in the treatment of DCM in only a few centers[24,25]. Thus, attention has recently been directed to the use of adrenoceptor partial agonists[12].

Xamoterol is a β_1-partial agonist with intrinsic sympathomimetic activity of 43% of the level of isoprenaline. When the sympathetic tone is low, it acts as a β-agonist; when sympathetic tone is high, it acts as a β-antagonist. Although xamoterol is devoid of any β-agonist effects, it has a β-antagonistic action when the dose is sufficient; the cardioselectivity ratio (β_1: β_2) as an antagonist is 16: 1. Thus, xamoterol will stabilize cardiac function against changes in sympathetic tone. Xamoterol may be useful in patients with heart failure with abnormally increased sympathetic tone and whose β-receptors are down-regulated[26,27].

β-receptors in lymphocytes have been commonly used for studies of down-regulation in heart failure for convenience[28,29]. Whether lymphocyte β_2-receptor changes correspond to changes in myocardial β_1-receptors is controversial.

In the present study, xamoterol increased Bmax and Kd of lymphocyte β-receptors in healthy volunteers and in patients with heart failure. This suggests that xamoterol up-regulated β-receptors both in healthy volunteers and in patients in heart failure, and this effect seemed to be related to a β-antagonist effect of the drug. In healthy volunteers, the drug increased blood pressure and FS, and these results seemed to be related to a β-agonist effect of the drug. In patients with heart failure, heart rate and FS were unaffected, but blood pressure rose, suggesting that the drug exerts a mild β-agonist effect even in patients with heart failure, when plasma norepinephrine level is about 0.51 ng/ml[30].

In the present study, when xamoterol was given to patients with DCM for 12 months, reduced CTR, increased EF and improved exercise tolerance were observed. Heart rate and pulmonary wedge pressure during exercise decreased or tended to decrease, while resting hemodynamics were unchanged. Some patients had EF greater than 40% before the study, because cardiac function in the patients improved by a rest for more than one month after diagnosis. Xamoterol increased Bmax of the lymphocyte β-receptors in DCM without adversely affecting cardiac function.

In our previous study, acute and chronic effects of xamoterol were evaluated in patients with heart failure in NYHA class II or III[30,31]. When xamoterol was administered intravenously, blood pressure, heart rate, CI and PAW were all unaffected acutely. Nevertheless, exercise tolerance and hemodynamics improved when the drug was given for long-term periods. These results indicated that xamoterol is ineffective in heart failure when given acutely, but gradually improves the condition when given over a prolonged period.

The present study showed that the density and affinity of lymphocyte β-receptors increased in patients with heart failure in NYHA class II or III following the treatment with xamoterol without adversely affecting cardiac function. This suggests that xamoterol may improve cardiac function by an appropriate effect of antagonist activity (preventing a cardiotoxic effect of catecholamines, normalizing down-regulated β-adrenergic pathways, suppressing exercise-induced tachycardia) and an agonist activity (increasing ventricular contractility).

We suppose that these combined effects of xamoterol, when given chronically to patients with heart failure, result in up-regulation of myocardial β-receptors, improve cardiac function, a decrease in plasma norepinephrine level and a decrease in arrhythmias.

The effect on mortality is crucial for evaluating a new drug for heart failure. Thus further studies of longer treatment will be needed to define whether xamoterol reduces mortality of patients with DCM.

要　約

拡張型心筋症における Xamoteral の効果：β受容体の増加

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Xamoterol (200 mg/日，partial-β_1-agonist) を健常者と心不全患者に7日間投与した．リンパ球β受容体は健常者に比して心不全患者で受容体数 (931±214 対 1466±373 sites/cell)，親和性 (0.60±0.11 対 1.07±0.14 nM) ともに低下していた．Xamoterol 投与後，両群で受容体数 (7169±3768, 7749±3807 sites/cell)，親和性 (6.01±3.84, 9.06±4.66 nM) はともに著明に上昇した（ともに $p<0.01$）．

Xamoterol (200 mg/日) を拡張型心筋症患者 (DCM) 10例に12ヵ月間投与し，3ヵ月後と12ヵ月後に検討した．心胸郭比は 57±6% から3ヵ月後 55±5%，12ヵ月後 54±5% に縮少し（ともに $p<0.05$），運動耐容能は 5±2 分から 7±2 分と 7±2 分へ増加した ($p<0.01$, $p<0.05$)．心エコー図法による左室内周短縮率も 13±6% から 20±8% ($p<0.01$) と 20±10% ($p<0.05$) へ増加した．同量運動負荷時の肺動脈楔入圧は 40±12 mmHg から3ヵ月後 25±9 mmHg に低下した ($p<0.01$)．運動負荷時心拍数は 118±9/分から3ヵ月後 106±6/分 に低下した ($p<0.01$)．しかし12ヵ月後のそれらは不変であった．投与3ヵ月，12ヵ月後にリンパ球β受容体数 (1024±413 から 1976±497, $p<0.01$, 1584±650 sites/cell, NS) と親和性 (0.67±0.27 から 1.60±0.42 $p<0.01$, 1.21±0.54 nM, $p<0.05$) の上昇がみられた．

Xamoterol を DCM に長期投与することにより，そのβ刺激作用とβ遮断作用が有効に作用し，運動耐容能，血行動態の改善がみられた．

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