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Risk factors and the effects of xamoterol in idiopathic dilated cardiomyopathy

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Summary

A long-term follow-up study was performed for 110 patients with idiopathic dilated cardiomyopathy (DCM) for 34±12 months (range 3–122 months). Thirteen patients died of heart failure, 15 of sudden death and one of non-cardiac death. The 3- and 5-year survival rates were 78 and 62%, respectively. The important factors in predicting the 3-year survival rate were left ventricular end-diastolic volume index (LVEDVI≥150 ml/m²=66%, <150 ml/m²=93%, $p<0.01$), myocardial cell diameter (>25 μm=42%, ≤25 μm=87%, $p<0.05$) and sustained ventricular tachycardia (VT present=32%, absent=85%, $p<0.01$).

In a prospective study, 26 patients with DCM were given a β_1-partial agonist, xamoterol (200 mg daily) and were followed for 35±15 months (6–53 months). The cardiothoracic ratio, left ventricular end-diastolic dimension and exercise heart rate decreased, and the exercise duration, fractional shortening and ejection fraction increased after xamoterol therapy. The 3-year survival rate was 83%.

These results suggest that the important factors in predicting the survival rate of DCM patients were LVEDVI, myocardial cell diameter and the occurrence of VT. Adjunctive xamoterol therapy in DCM had a beneficial effect on hemodynamics and symptoms.

Key words

Xamoterol Beta$_1$-partial agonist Risk factor Dilated cardiomyopathy

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Introduction

The long-term prognosis of idiopathic dilated cardiomyopathy (DCM) is extremely poor. Fuster et al[1] have reported that the 5-year survival rate of DCM patients is 38%. Currently, DCM is treated mainly by the potentiation of cardiac contractile force using cardiotonics and by decreasing the cardiac work load using diuretics or vasodilators, however, the therapeutic effects of these forms of treatment are not always satisfactory[2,3]. It would be desirable to identify high and low risk groups at the times of diagnosis.

In patients with DCM, a decreased cardiac function increases the catecholamine level in the blood, which may adversely affect the myocardium and further lower the cardiac contractile force[4]. Waagstein et al have reported that β-blockers are useful for DCM patients with heart failure, and followed their subjects with several studies to confirm their results[5].

Xamoterol (ICI 118, 587) is a partial agonist which acts on β-receptors, and it has 43% of the maximum activity of isoprenaline[6]. When sympathetic tone is relatively high, xamoterol acts as an antagonist. Due to its pharmacological properties, xamoterol apparently stabilizes the response of the heart to sympathetic stimulation. Thus, xamoterol is considered useful for DCM patients, because it may improve cardiac function through its mild potentiating action on cardiac contraction and because it may protect the heart from the cardiotoxic effects of excessive catecholamines[6,7].

In the present study, the risk factors which determine the survival rates and long-term effects of xamoterol in patients with DCM were examined.

Materials and methods

1. Factors for determining the survival rates of DCM patients

From 1977 to 1986, 110 patients were diagnosed as having DCM by cardiac catheterization, endomyocardial biopsy and echocardiography according to the diagnostic criteria of WHO/ISFC, and followed up at Niigata University, Tachikawa Hospital, Kuwana Hospital and Sannocho Hospital[8]. They consisted of 80 males and 30 females, whose ages ranged from 12 to 76 years (mean±1SD; 54±12 years). Forty-eight, 45 and 17 patients were diagnosed as New York Heart Association (NYHA) functional classes II, III and IV, respectively. Sixty-five patients had sinus rhythm and 45 had atrial fibrillation.

The coronary arteries of all patients were normal. Secondary cardiomyopathy, such as myocarditis, was excluded by endomyocardial biopsy. The patients had been treated with conventional therapy for cardiac failure or arrhythmia using digitalis, diuretics, vasodilators and antiarrhythmics. The follow-up period ranged from 3 to 122 months (34±12 months).

2. Effects of xamoterol in patients with DCM

From 1985 to 1987, 86 patients were diagnosed as having DCM. Randomly, 26 patients were enrolled in the present study. They consisted of 20 males and 6 females, whose ages ranged from 26 to 71 years (53±12 years). Ten, 15 and one patients were diagnosed as NYHA functional classes II, III and IV, respectively.

After ascertaining by one month of monitoring that the subjective symptoms of the patients were stable, they were incorporated into the present study. Prior to entering the study, it was fully explained to all patients, and oral informed consent to the study was obtained from them.

Xamoterol 100 mg was administered b.i.d. (200 mg/day). Conventional therapy, such as digitalis, diuretics, vasodilators and anticoagulants, was continued throughout this study without modification of dosage and administration as much as possible. Patients who had been treated with β-stimulants or β-blockers were excluded from the study. One patient, who was NYHA functional class IV, received xamoterol 50 mg b.i.d. (100 mg/day) for the first 7 days, then 100 mg was administered b.i.d. from the 8th day on. The patients were treated with xamoterol for 6–53 months (35±15 months).

The norepinephrine concentration in the

blood and the β-receptor density in lymphocytes were determined in 8 patients. As previously reported, the norepinephrine concentration was determined by high performance liquid chromatography; whereas, the density of β-receptors in lymphocytes isolated from 10 m*l* blood was measured by radioligand binding assay with ^{125}I-iodocyanopindolol[9].

Ventricular tachycardia (VT) was confirmed by 24-hour Holter electrocardiographic monitoring (Holter ECG), and we considered sustained VT if it lasted ≥30 sec.

Left ventricular end-diastolic dimension (LVDD) and left ventricular end-systolic dimension were determined by echocardiography, and the left ventricular fractional shortening (FS) and left ventricular ejection fraction (EF) were calculated.

Exercise tolerance was determined in 26 patients (the tolerance time of NYHA functional class IV patients was determined as 0 min) by an exercise test with a supine bicycle ergometer. The load was begun with 25 watts and was gradually increased by 25 watts at 3-min intervals (multistage loading method), and the test was discontinued when subjective symptoms, such as dyspnea, fatigue, hypotension and chest pain or severe arrhythmias developed.

Hemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were measured by inserting a Swan-Ganz catheter into the femoral vein. The left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-diastolic pressure (LVEDP) were measured by cardiac catheterization.

Subjective symptoms, NYHA functional classes, physical parameters and hemodynamic parameters were recorded at 6–18 month intervals.

3. Statistical analyses

The cumulative survival curve was drawn using the Kaplan-Meier method. The survival rates were compared using the generalized Wilcoxon test for the xamoterol group and for the 110 patients with DCM. Variables considered for confounding included age, cardiothoracic ratio, CI, EF, LVEDVI, LVEDP, myocardial cell diameter of the right ventricle and sustained VT. When the p value was less than 0.05, the difference was regarded as statistically significant. All data obtained were expressed as means±1SD.

Results

1. Survival curves and risk factors of 110 patients with DCM

1. The 3- and 5-year survival rates: The 3- and 5-year survival rates of the 110 patients were 78 and 62%, respectively (**Fig. 1**).

Twenty-nine patients died during the follow-up study; 13 (45%) died of heart failure, 15 (52%) died suddenly, one (3%) died of a non-cardiac event.

2. Risk factors (**Table 1, Fig. 2**): Survivors tended to be older than non-survivors (56±12 vs 50±17 years, $p<0.05$).

Survivors had higher CI values (3.0±0.9 vs 2.4±0.8 *l*/min/m^2, $p<0.05$) and lower values for LVEDVI (123±48 vs 184±38 m*l*/m^2, $p<0.01$), LVEDP (13±9 vs 18±9 mmHg, $p<0.05$) and cell diameter (21.5±3.4 vs 28.1±5.3 μm, $p<0.01$). Holter ECGs demonstrated sustained VT in 2 (2%) among 81 survivors and in 6 (21%) of 29 non-survivors ($p<0.01$). Other variables,

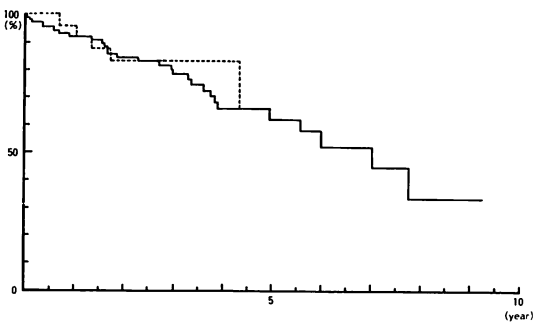

Fig. 1. Cumulative survival rate curves (Kaplan-Meier) **of patients with idiopathic dilated cardiomyopathy.**

Patients were treated with conventional therapy (non-xamoterol, solid line, n=110) or with xamoterol adjunctive to conventional therapy (dotted line, n=26).

Table 1. Comparison between baseline clinical and hemodynamic variables in survivors (n=81) and non-survivors (n=29)

	Survivors	Non-survivors
Age (yrs)	56±12	50±17*
Sex (male/female)	57/24	23/6
Cardiothoracic ratio (%)	59±8	61±8
Fractional shortening (%)	15±5	14±7
LVEDDI (cm/m^2)	4.2±0.7	4.4±0.7
CI (*l*/min/m^2)	3.0±0.9	2.4±0.8*
Ejection fraction (%)	34±11	30±13
LVEDVI (m*l*/m^2)	123±48	184±38**
LVEDP (mmHg)	13±9	18±9*
Cell diameter (μm)	21.5±3.4	28.1±5.3**
Sustained VT	2 (2%)	6(21%)*
Non-sustained VT	39(48%)	15(52%)

LVEDDI=left ventricular end-diastolic dimension index; CI=cardiac output index; LVEDVI=left ventricular end-diastolic volume index; LVEDP=left ventricular end-diastolic pressure; VT=ventricular tachycardia.
* $p<0.05$, ** $p<0.01$ vs survivors.

such as cardiothoracic ratio, FS, EF and non-sustained VT were not significant risk factors. The factors for determining the 3-year survival rate were LVEDVI ($\geq$150 m*l*/m^2=66%, <150 m*l*/m^2=93%, $p<0.01$), myocardial cell diameter (>25 μm=42%, $\leq$25 μm=87%, $p<0.05$) and sustained VT (present=32%, absent=85%, $p<0.01$).

2. Xamoterol therapy in 26 patients

1. Survival curve and clinical course (**Fig. 1**): The 3-year survival rates of the basal treatment group and of the basal treatment plus xamoterol group were 78 and 83%, respectively. Thus, there was no significant difference between the 2 groups.

Three patients died of heart failure after they were treated with xamoterol during 7, 21, and 22 months, respectively. Two patients died suddenly after they were treated with xamoterol for 15 and 45 months, respectively.

2. Long-term effects of xamoterol in all 26 patients (**Table 2**): No worsening of heart failure, and no new development of arrhythmias or hypotension was observed in any patients during the first 3 months of xamoterol therapy, allowing xamoterol therapy to be continued for 6 months or longer. Twenty-one of 26 patients survived and one dropped out of the study at 7 months. The NYHA classification of 13 out of the 20 survivors improved from 2.8±0.5 to 1.7±0.5 ($p<0.001$).

Holter ECGs demonstrated ventricular premature contractions in all 26 patients, and sustained VT in 9 before xamoterol therapy. Sustained VT resolved in 3 of the 9 patients after xamoterol therapy, and no new development of sustained VT was observed in the other patients.

The cardiothoracic ratio was reduced significantly from 58±8% before xamoterol therapy to 54±7% thereafter ($p<0.05$). Mean exercise duration increased from 5.6±2.3 to 7.2±2.2 min ($p<0.05$). LVDD in echocardiography decreased from 6.2±0.9 to 5.8±1.0 cm ($p<0.05$). FS increased from 14±7 to 21±10% ($p<0.05$). EF increased from 26±11 to 37±15% ($p<0.05$). The exercise heart rate decreased significantly from 126±18 to 112±16 beats/min ($p<0.01$).

After xamoterol therapy, the resting heart rate (from 78±18 to 74±14 beats/min), systolic blood pressure (from 119±17 to 127±17

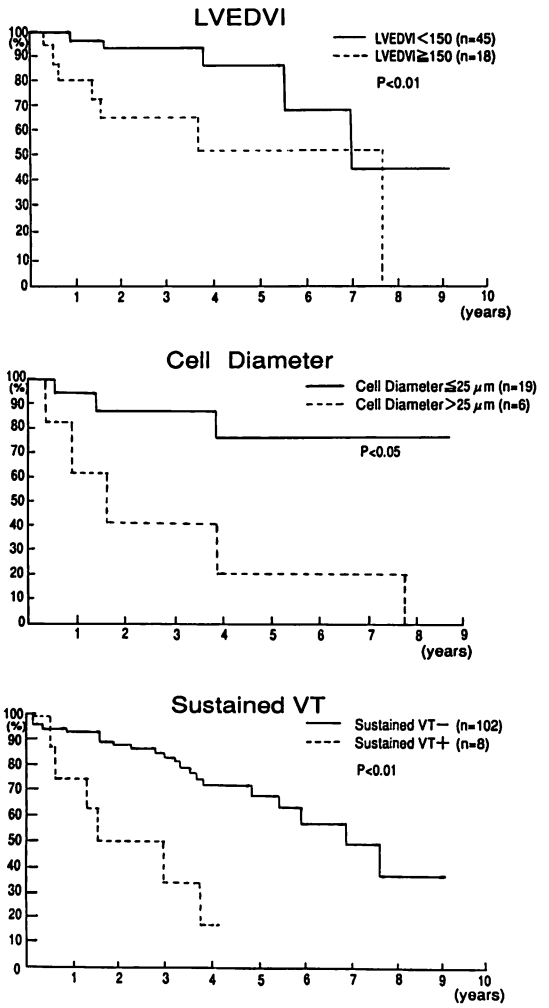

Fig. 2. Cumulative survival rate curves of patients with idiopathic dilated cardiomyopathy.

The malignant factors were left ventricular end-diastolic volume index (LVEDVI≥150 ml/m²), right ventricular myocardial cell diameter (>25 μm) and sustained ventricular tachycardia (VT).

mmHg), norepinephrine (from 0.52±0.27 to 0.49±0.28 ng/ml), density of β-receptors in lymphocytes (from 1,024±413 to 1,584±650 sites/cell), CI (from 2.41±0.39 to 2.48±0.37 l/min/m²) and PCWP (from 16±5 to 14±6 mmHg) did not change significantly.

3. Comparisons between survivors and non-survivors (**Table 3**): The age, exercise tolerance time, heart rate, blood pressure, LVDD, FS, EF, CI and PCWP at the start of xamoterol therapy did not differ significantly between the survivors and non-survivors.

Cardiothoracic ratio (from 56±7 to 53±6, $p<0.05$), exercise tolerance (from 5.8±2.4 to 7.7±2.2 min, $p<0.01$), LVDD (from 6.1±0.8 to 5.6±0.8 cm, $p<0.01$), FS (from 14±7 to 23±10%, $p<0.01$), EF (from 26±12 to 40±15%, $p<0.05$) and PCWP (from 15±4 to 12±4 mmHg, $p<0.05$) were improved after xamoterol therapy in survivors, but were unchanged in non-survivors. The heart rate after exercise decreased after xamoterol therapy both in the survivors (from 122±15 to 108±15 beats/min, $p<0.01$) and the non-survivors (from 143±21 to 112±19 beats/min, NS). However, between the 2 groups there were no significant differences.

The systolic blood pressure (139±17 vs 116±13 mmHg, $p<0.05$), LVDD (5.6±0.8 vs 6.7±0.9 cm, $p<0.05$), FS (23±10 vs 12±3%, $p<0.05$), EF (40±15 vs 23±4%, $p<0.05$), norepinephrine (0.37±0.14 vs 0.85±0.25 ng/ml, $p<0.05$) and PCWP (12±4 vs 20±7 mmHg, $p<0.05$) were significantly different between the survivors and non-survivors.

The norepinephrine concentration before xamoterol therapy was 0.41±0.21 and 0.65±0.36 ng/ml in survivors and non-survivors, respectively, indicating higher levels in both groups than in healthy subjects (0.23±0.08 ng/ml)[10], however, no significant difference was noted between the survivors and non-survivors. After xamoterol therapy, the norepinephrine concentration of survivors was reduced to 0.37±0.14 ng/ml; whereas, that of non-survivors was maintained at a relatively high level (0.85±0.25 ng/ml). As a result, the norepinephrine after xamoterol therapy was significantly higher in non-survivors than in survivors ($p<0.05$).

The density of β-adrenergic receptors in lymphocytes before xamoterol therapy was lower in survivors and non-survivors than in healthy subjects (1,466±373 sites/cell)[9]. The

Table 2. Long-term effects of xamoterol in 26 patients

	Baseline	Long-term
Ventricular tachycardia (no.)	9	6
Cardiothoracic ratio (%)	58±8	54±7*
Exercise tolerance (min)	5.6±2.3	7.2±2.2*
Left ventricular diastolic dimension (cm)	6.2±0.9	5.8±1.0*
Fractional shortening (%)	14±7	21±10*
Ejection fraction (%)	26±11	37±15*
Exercise heart rate (beats/min)	126±18	112±16**
Resting heart rate (beats/min)	78±18	74±14
Systolic blood pressure (mmHg)	119±17	127±17
Norepinephrine (ng/m*l*)	0.52±0.27	0.49±0.28
β-receptor (sites/cell)	1,024±413	1,584±650
Cardiac index (*l*/min/m^2)	2.41±0.39	2.48±0.37
Pulmonary capillary wedge pressure (mmHg)	16±5	14±6

* $p<0.05$, ** $p<0.01$ vs baseline.

Table 3. Comparison between baseline and long-term treatment clinical and hemodynamic variables in survivors (n=20) **and non-survivors** (n=5)

	Baseline		Long-term treatment	
	Survivors	Non-survivors	Survivors	Non-survivors
Age (yrs)	52±12	57±10		
NYHA functional class (no.)				
I	0	0	4	0
II	9	1	14	2
III	10	4	2	1
IV	1	0	0	2
Cardiothoracic ratio (%)	56±7	64±8	53±6*	60±7
Exercise tolerance (min)	5.8±2.4	5.2±2.0	7.7±2.2**	5.6±1.5
Resting heart rate (beats/min)	67±9	75±27	66±6	77±23
Exercise heart rate (beats/min)	122±15	143±21	108±15**	112±19
Resting systolic blood pressure (mmHg)	129±21	114±16	139±17	116±13#
Atrial fibrillation (no.)	8	1	9	1
Ventricular tachycardia (no.)	7	2	4	2
Left ventricular end-diastolic dimension (cm)	6.1±0.8	6.9±1.0	5.6±0.8**	6.7±0.9#
Fractional shortening (%)	14±7	14±3	23±10**	12±3#
Ejection fraction (%)	26±12	27±6	40±15*	23±4#
Norepinephrine (ng/m*l*)	0.41±0.21	0.65±0.36	0.37±0.14	0.85±0.25#
β-receptor (sites/cell)	1,130±484	847±119	1,849±645	1,142±348
Cardiac index (*l*/min/m^2)	2.51±0.50	2.34±0.16	2.50±0.33	2.42±0.49
Pulmonary capillary wedge pressure (mmHg)	15±4	19±4	12±4*	20±7#

* $p<0.05$, ** $p<0.01$ vs baseline; # $p<0.05$ vs survivors.

density of β-receptors in survivors was increased into the normal zone during xamoterol therapy, from 1,130±484 to 1,849±645 sites/cell; whereas, that of non-survivors during xamoterol therapy was lower than that of healthy subjects.

Discussion

The long-term prognosis of DCM is extremely poor. In the present study, the 3- and 5-year survival rates were 78 and 62%, respectively, in 110 patients with DCM, and the 3-year survival rate of patients with sustained VT was very low (32%). So far, the etiology of DCM has not been clarified. Therefore, only symptomatic therapy has been given to DCM patients. Digitalis, diuretics, vasodilators and oral cardiotonics have been prescribed for heart failure. Antiarrhythmics have also been prescribed for a variety of arrhythmias, however, the risk of sudden death has not been mitigated. Although new therapies with implantable defibrillators or electrical ablation have been introduced, their therapeutic value has not yet been established[11,12]. However, cardiac transplants have been used to treat DCM patients with satisfactory therapeutic effects. In the present study, the malignant factors for determining the survival rate were LVEDVI ($\geq$150 ml/m^2), myocardial cell diameter (>25 μm) and sustained VT. The patients who have these malignant factors may be the ones who undergo heart transplantation, but cardiac transplantations are applicable only to a limited number of patients in a limited number of institutions at the present time.

Oral cardiotonics have been developed recently, and their clinical usefulness for treating chronic cardiac failure has been examined[13,14]. Although the short-term effects of these cardiotonics on hemodynamics are widely accepted, the usefulness of their long-term therapy and their usefulness for improving the prognosis of DCM patients have not been definitely established. Rather, they can possibly worsen the prognosis of DCM patients by promoting exhaustion of the myocardium with its already lowered contractility, or by inducing a fatal arrhythmia.

Intriguingly, it has been reported that β-blockers are useful for DCM patients[15,16]. It is argued that β-blockers are effective at least for a certain type of DCM patients, because β-blockers may improve the diastolic performance of the myocardium and protect the myocardium from excessive catecholamines[17]. Generally, however, β-blockers are considered to worsen cardiac failure through the suppression of cardiac function, therefore, they have been prescribed for DCM patients in only a limited number of clinical institutions. Since cardiac failure can be worsened during the early stage of β-blocker therapy, treatment can be started only with low doses, increasing the dosage carefully and gradually, while monitoring the patients' symptoms.

Xamoterol, a β_1-partial agonist, is approximately 0.43 times as potent as isoprenaline in agonist activity. Therefore, xamoterol may improve or maintain the cardiac function of a failing heart through its mild myocardial stimulation and protect the myocardium from excessive catecholamines.

In our other study[10], we examined the short-term effects of intravenous xamoterol in 13 patients with DCM. As a result, no significant changes were observed at rest either in survivors or in non-survivors. This result may be explained by the partial agonist activity of xamoterol, because the blood norepinephrine concentration of the patients in the present study was 0.52±0.27 ng/ml at rest[9,10]. HR at exercise was significantly decreased after intravenous xamoterol therapy. PCWP, CI, BP and HR at rest were unchanged after intravenous xamoterol administration, even in patients with high blood norepinephrine concentrations of not less than 0.70 ng/ml at rest. This indicates that the β-blocking activity of xamoterol at rest is relatively mild. Therefore, it is reasoned that the mild stimulatory and protective effects of xamoterol on the myocardium combined enable its safe application in DCM patients. Thus, we have begun long-term xamoterol therapy in DCM patients.

The long-term effects of oral xamoterol, 200 mg/day, were observed in 26 patients with DCM. Subjective symptoms and the NYHA functional classes of 20 patients were improved after 1–3 months of xamoterol therapy, and the therapeutic effects of xamoterol were maintained or augmented thereafter in most patients during long-term xamoterol therapy. These results showed that long-term xamoterol therapy improved the quality of life of DCM patients without producing tachyphylaxis. The data following long-term xamoterol therapy were compared between the survivors and non-survivors. A variety of parameters before xamoterol therapy did not differ significantly between the survivors and non-survivors. In contrast, after xamoterol therapy, the blood norepinephrine concentration, LVDD and PCWP were reduced while the density of β-receptors in lymphocytes, FS and EF were increased in the survivors compared with the non-survivors.

The survival rate was compared using the generalized Wilcoxon test between xamoterol therapy and non-xamoterol therapy. The 3-year survival rates for the basal treatment group and the basal treatment plus xamoterol group were 78 and 83%, respectively, indicating no significant difference between the 2 groups (**Fig. 1**). It has been reported that the 3-month survival probabilities for a xamoterol group and a placebo group are 91 and 96%[18], respectively. In that study, patients with severe heart failure (NYHA III and IV) were treated with xamoterol 200 mg twice daily. In the present study, patients were treated with xamoterol 100 mg twice daily. And one patient who was a NYHA functional class IV received xamoterol 50 mg twice daily during the first 7 days, and 200 mg/day thereafter. It is important that small doses of xamoterol should be administered to patients with heart failure, similar to β-blocker treatment[17]. Further, cardiac transplantation needs to be applied in the treatment of DCM patients with malignant features.

It is difficult to predict the therapeutic effects of xamoterol prior to beginning its administration. However, it is expected that xamoterol will be effective in improving prognosis and improving such parameters as LVDD, FS, EF, blood norepinephrine concentration and PCWP.

要　約

拡張型心筋症の予後不良因子と xamoterol の効果

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拡張型心筋症 (DCM) 110例を長期観察し，予後不良因子を検討した．34±12ヵ月 (3-122ヵ月) の観察で，心不全死13例，突然死15例，非心臓死1例がみられ，3年生存率 78%，5年生存率 62% であった．3年生存率への重要因子は左室拡張末期容量係数 ($\geq$150 ml/m^2=66%，$<$150 ml/m^2=93%，$p<0.01$)，心筋横径 ($>25\ \mu$m=42%，$\leq 25\ \mu$m=87%，$p<0.05$)，持続型心室頻拍(有=32%，無=85%，$p<0.01$) であった．

Xamoterol 200 mg/日を DCM 26例に 35±15ヵ月 (6-53ヵ月) 間投与し，長期効果を検討した．投薬後心胸比，左室拡張末期径，運動時心拍数は減少し，運動耐容能，左室内径短縮率，駆出率は増加した．3年生存率は 83% であった．

DCM で予後不良因子は左室拡張末期容量 ($\geq$150 ml/m^2)，心筋横径 ($>25\ \mu$m)，持続型心室頻拍であった．Xamoterol は DCM 患者の血行動態や症状を改善した．

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