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The prognostic significance of left ventricular response to isoproterenol infusion in patients with dilated cardiomyopathy

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Summary

To evaluate the prognostic value of the left ventricular response to isoproterenol infusion in patients with dilated cardiomyopathy (DCM), 25 patients, 17 men and eight women, were studied.

According to responses of left ventricular function to isoproterenol (0.02 μg/kg/min), the patients were classified in two groups: the normal response group, in which fractional shortening increased by more than 10% (n=10); and the low response group, in which fractional shortening increased by 10% or less (n=15). A follow-up spanning four to 40 months with an average of 21 months disclosed that six patients died, two deteriorated, and six had no change in the low response group, while seven patients were improved, three stabilized, and no one deteriorated or died in the normal response group. There was a difference in the clinical courses of the two groups.

Thus, the left ventricular response to isoproterenol proved useful in predicting the course of DCM.

Key words

Isoproterenol Dilated cardiomyopathy Prognosis

Introduction

Dilated cardiomyopathy (DCM) is an entity consisting of dilated ventricles and impairment of cardiac function of unknown cause[1,2]. Specific therapy is not yet available and prognosis of patients with the disease is reportedly extremely poor[3,4]. However, some recent studies have shown that a considerable number of such patients have improved[5~7]. Thus, the prognosis of DCM is generally thought to vary. Predictive prognostic factors in DCM reportedly

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include age, sex, duration of symptoms, alcohol consumption and hypertension; cardiothoracic ratio on chest radiography; left ventricular end-diastolic pressure and volume, cardiac index, ejection fraction on cardiac catheterization; left ventricular end-diastolic dimension and fractional shortening on echocardiography; atrial fibrillation, ventricular arrhythmias and left conduction delay on electrocardiography; cell diameter and percent fibrosis by endomyocardial biopsy[4~11]. These are important factors for patients' conditions, but they often fail to predict the clinical course. This suggests that cardiac evaluations only in the resting state are inadequate and that additional evaluations under conditions of stress may be necessary. However, patients with DCM cannot easily undergo exercise stress tests, because of the high incidence of fatal arrhythmias during exercise and deterioration and ensuing heart failure after exercise. In our institute, instead of exercise, low dose isoproterenol infusion (0.02 μg/kg/min) under electrocardiographic monitoring and echocardiography has been accepted as a preferable stress test for high risk patients[12,13]. The advantage of the low dose isoproterenol infusion test is safety, because the stress is mild and the heart rate (HR) will return to its pre-infusion level one or two minutes post-infusion.

In the present study, the clinical courses of patients with DCM were followed, and the prognostic significance of the left ventricular response to isoproterenol infusion was assessed.

Patients and Methods

In the present study, 25 DCM patients, 17 men and 8 women, whose mean age was 55 years were observed. Each of the 25 patients had echocardiographic left ventricular dilatation evidenced by enlarged ventricular end-diastolic dimension (LVDd $>$ 50 mm), and disordered left ventricular wall motion evidenced by decreased fractional shortening (FS $<$ 25%) due to unknown cause. Patients with specific diseases of cardiac muscle, infectious or metabolic, systemic diseases of connective tissue heredofamilial disorders, and hypersensitivity or toxic reactions were excluded. History taking and physical examination were performed for all patients by two physicians. Interpretations of the electrocardiograms, chest radiographs, angiograms, and other studies were performed by at least two observers. Functional status of each patient was judged according to the classification of New York Heart Association (NYHA). All patients received posteroanterior and lateral chest radiography at the initial admission. A cardiothoracic ratio of $>$0.50 was considered evidence of cardiomegaly by chest radiography. At the time of admission, 12-lead electrocardiogram was recorded using simultaneous 3-channel recorder. Coronary angiography was performed for 12 patients with suspected coronary artery disease, but none had stenosis greater than 50% in any of the major coronary arteries or their branches. Six patients had histories of mild hypertension, and five long term histories of consuming a small amounts of alcohol. Three patients had influenza-like symptoms shortly before the first documentation of cardiomegaly, but there was no serological evidence of such involvement. Six patients had mild or moderate mitral regurgitation with no echocardiographic evidence of rheumatic changes in the mitral valves.

Echocardiographic study:

Echocardiograms were recorded using a Toshiba SSH-11A with a 2.4 MHz transducer focused at 7.5 cm. The M-mode echocardiograms were recorded using a Honeywell 1219 strip chart recorder at a paper speed of 50 mm/sec, together with electrocardiogram and phonocardiograms. All echocardiograms were obtained with patients in a slight left lateral position. The transducer was placed at the third or fourth intercostal space at the left sternal border. Left ventricular echocardiograms were monitored by two-dimensional echocardiography and recorded at the level of the chordae tendineae just below the tip of the mitral leaflets. Recordings were made during held expiration, and care was taken to avoid involuntary Valsalva maneuvers. From the recorded echocardiograms, LVDd and left ventricular end-systolic dimensions

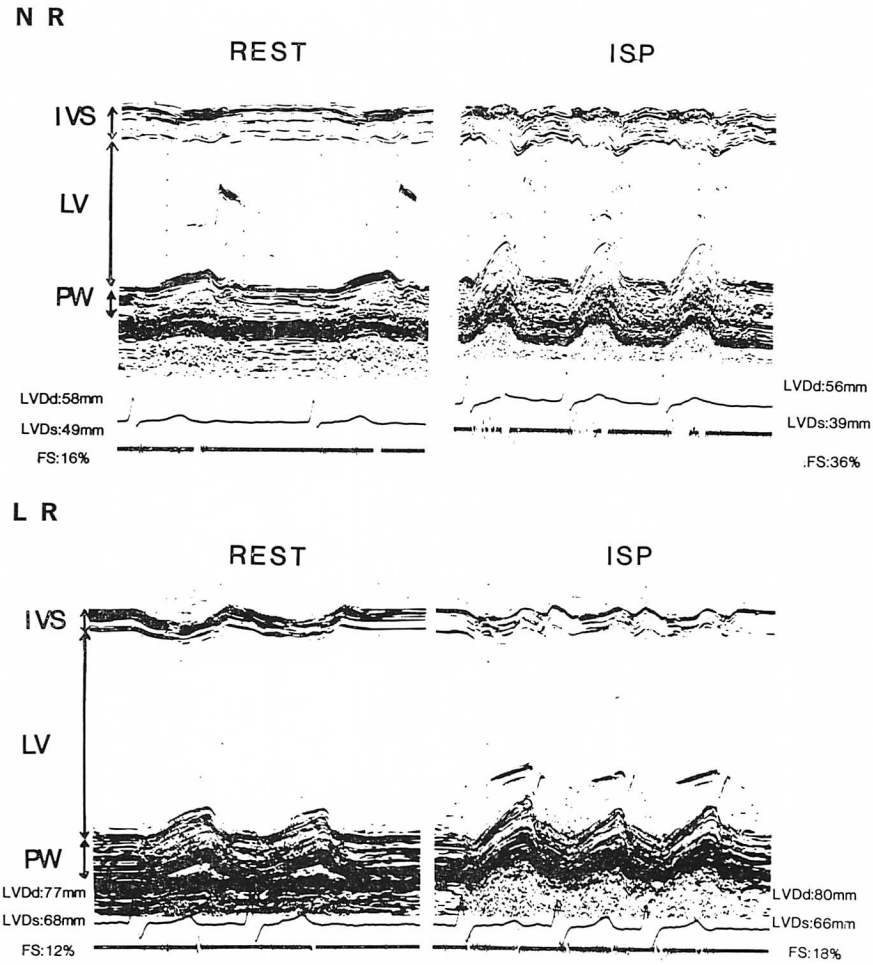

Fig. 1. Illustrative echocardiograms showing the changes after isoproterenol infusions in both groups.

FS increases from 16% to 36% in the normal response group (NR: top), and from 12% to 18% in the low response group (LR: bottom).

Abbreviations: NR=normal response group; LR=low response group; IVS=interventricular septum; PW=posterior wall of the left ventricle; LV=left ventricle.

(LVDs) were measured and FS was calculated as follows: (LVDd−LVDs)/LVDd×100.

Infusion of isoproterenol:

Isoproterenol 0.02 μg/kg/min was intravenously infused for five min using a calibrated infusion pump. During infusion, electrocardiograms were monitored simultaneously. Before and after 5 min infusion of isoproterenol, echocardiograms, electrocardiograms, and phonocarddiograms were recorded. Blood pressure (BP) was measured using a cuff and mercury column sphygmomanometer. When their HR increased to 85% of their target HR five min before infusion, the infusion was discontinued immediately.

Patient's classification:

Table 1. Patients' data

Group	Patient No.	Age·Sex	NYHA funct. class	LVDd	LVDs	FS	⊿FS	ECG
NR	1	38 M	I	34	42	22	17	
	2	46 F	I	53	36	32	17	
	3	62 M	II	55	35	25	11	
	4	53 M	I	75	66	12	12	af
	5	56 M	I	52	42	25	13	af
	6	66 M	I	57	43	25	13	
	7	53 F	I	58	49	16	20	af
	8	44 F	II	63	53	16	12	
	9	57 M	I	77	65	16	20	
	10	49 F	II	60	53	12	16	af
	Mean	52±8		60±8	48±10	19±7	15±3	
LR	11	52 M	II	76	68	11	−3	
	12	69 F	I	52	38	27	−1	
	13	64 F	II	64	58	9	9	
	14	39 M	I	50	34	34	9	
	15	45 M	II	75	70	7	3	af
	16	79 M	I	66	58	12	2	af
	17	56 M	I	79	63	20	4	af
	18	61 M	II	67	58	13	5	af
	19	57 M	II	77	68	12	6	af
	20	62 F	II	65	60	8	5	
	21	68 F	I	75	70	10	8	af
	22	65 N	I	66	53	20	−3	
	23	65 F	I	55	47	15	1	af
	24	41 F	II	60	57	5	5	af
	25	64 M	I	84	76	10	−3	
	Mean	59±11		68±10	59±11	14±7	3±5	

Abbreviations: NYHA=New York Heart Association; LVDd=left ventricular end-diastolic dimension; FS=fractional shortening; af=atrial fibrillation.

According to the left ventricular response to isoproterenol, that is, the change of FS (⊿FS) by isoproterenol infusion, patients were classified in two groups: patients with ⊿FS more than 10%, as the normal response group; and patients with ⊿FS of 10% or less, as the low response group (**Fig. 1**). Because the average value of ⊿FS in normal healthy persons in our previous study[14] was 14±3% after five min infusion of isoproterenol 0.02 μg/kg/min, a 10% increase of FS was regarded as the discriminating level.

Evaluation of clinical course:

Follow-up study for a mean of 21 months (range 4 to 40 months) was performed by analysis of clinical and echocardiographic data. Follow-up extended from the date of the isoproterenol infusion test to the latest data collection at the patient's death. No patients were lost to follow-up. The echocardiographic criteria prognostic of patient's conditions were: ① an increase of FS by more than 5% or a decrease of LVDd by more than 10% of a preinfusion value, ② a decrease of FS by more than 5% or

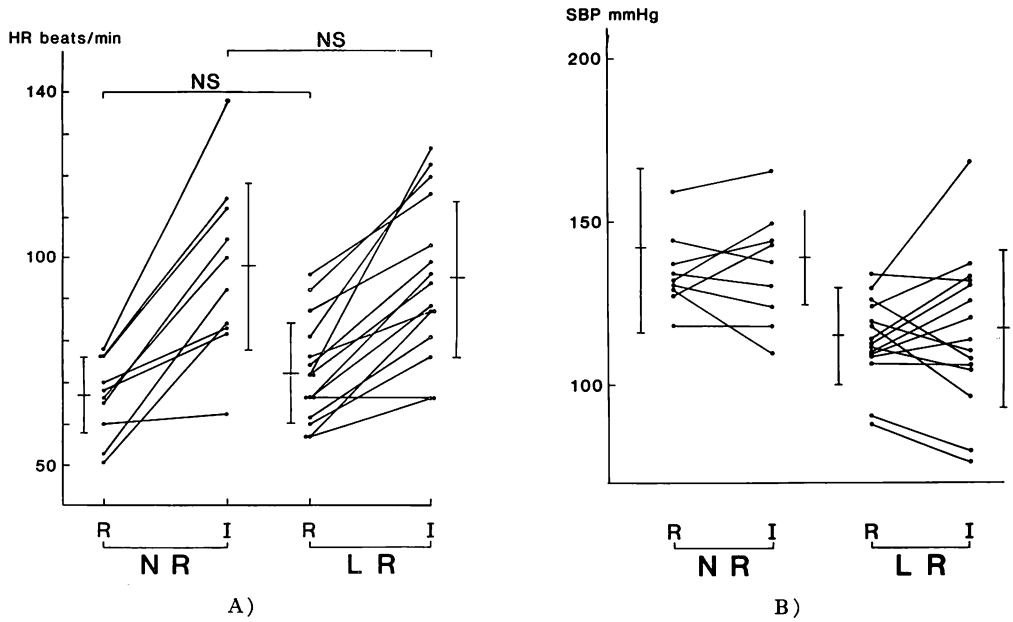

Fig. 2. Hemodynamic changes induced by isoproterenol infusion.
Left: changes in systolic blood pressure (SBP). Right: changes in heart rate (HR).
NR=normal response group; LR=low response group; R=rest; I=isoproterenol infusion.

an increase of LVDd by more than 5%, or death. ③ No change was signified by no change of these measurement.

Medications:

Medications during the present study included digitalis preparation for 19 patients, diuretics for 24, and antiarrhythmic drugs for four (disopyramide, 2; mexiletine, 2). Six patients received antiplatelet-aggregating agents (dipyridamole, 4; aspirin, 2). Nitrate was used for vasodilator therapy in one. Propranolol was not used, though it is reportedly effective in some patients with DCM[15].

Statistics:

The data were analyzed using the Student's t test. Probability values <0.05 were used to indicate significance of differences. All data were presented as means$\pm$SDs.

Results

Individual and mean clinical, echocardiographic and electrocardiographic data are shown in **Table 1.** Mean age was 59 ± 6 years in the normal response group and 53 ± 4 years in the low response group, and there was no significant difference between these two groups. At the times of isoproterenol infusion test, all patients were in the NYHA class 1 or 2. In the normal response group, seven patients were in the NYHA class 1 and three in class 2. In the low response group, eight patients were in NYHA class 1, and seven, in class 2. Four of 10 patients in the normal response group and eight of 15 in the low response group had atrial fibrillation.

Hemodynamics

Fig. 2 shows hemodynamic data before and during isoproterenol infusions. In the normal response group, HR increased from 67 ± 9 bpm to 98 ± 20 bpm ($p<0.01$) and systolic blood pressure (SBP) decreased from 142 ± 20 mmHg to 139 ± 11 mmHg. In the low response group, HR increased from 72 ± 12 bpm to 95 ± 19 bpm and SBP increased from 114 ± 15 mmHg to

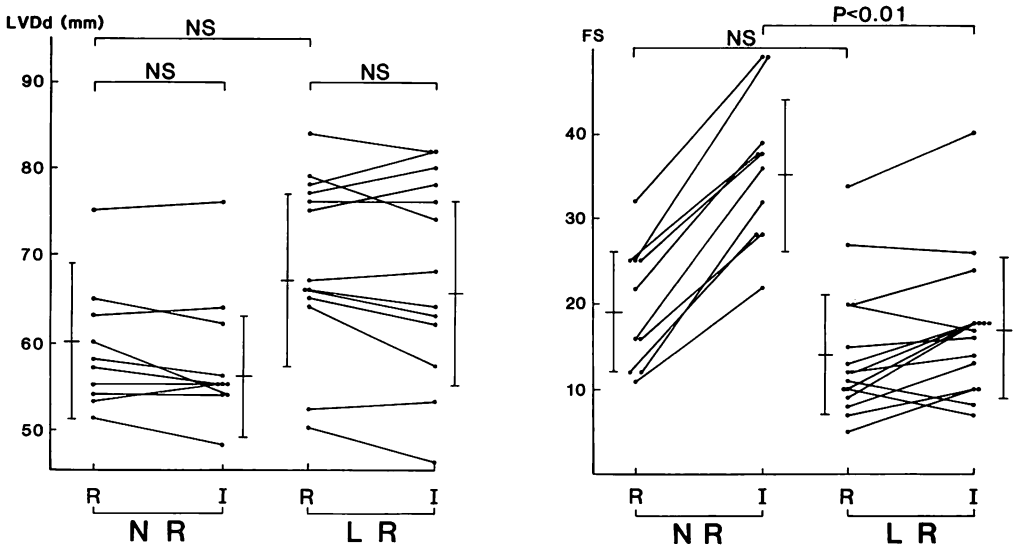

Fig. 3. Echocardiographic changes induced by isoproterenol infusion.

Left: changes in left ventricular end-diastolic dimension (LVDd). Right: changes in fractional shortening (FS).

NR=normal response group; LR=low response group; R=rest; I=isoproterenol infusion.

Table 2. Echocardiographic findings and prognosis

LVDd	Number of patients		
	I	NC	D
50~60 mm	3	5	2
61~70 mm	4	3	2
71~ mm	1	2	4

LVDd=left ventricular end-diastolic dimension; I=improved; NC=no change; D=deteriorated.

Table 3. Left ventricular response to isoproternol and prognosis

Group	Clinical course	Number of patients
NR	Improved	7
	No change	3
	Deteriorated	0
LR	Improved	1
	No change	6
	Deteriorated	8
	(Death	6)

NR=normal response group; LR=low response group.

122±24 mmHg. As SBP showed no significant change, afterload of the left ventricle post-infusions did not differ significantly from that in the pre-infusion state.

Echocardiographic findings:

The changes of LVDd and FS are shown in **Fig. 3.** In the normal response group, LVDd was 60±8 mm before infusions and 56±7 mm after infusions. In the low response group, LVDd was 68±10 mm before infusions and 66±11 mm after infusions. There were no significant differences between the groups before and after infusions. LVDd values before and after infusions were nearly the same. FS did not differ significantly between the two groups before infusions. FS increased from 19±7%

to 35±9% in the normal response group, and did so from 14±7% to 17±8% in the low response group. Ventricular premature contractions developed in nine patients. Results of analyses of the arrhythmia data will be reported separately.

Clinical course and prognosis:

The echocardiographic findings and prognoses of DCM are shown in **Table 2.** Among seven patients with markedly dilated left ventricles (70 mm<LVDd), one was improved, two did not change, and four deteriorated. Among 11 patients with mildly dilated left ventricle (50 mm<LVDd<60 mm), three were improved, five did not change, and two deteriorated. These findings suggest that the prognosis is not predictable by left ventricular dimensions.

Table 3 shows the prognosis of the two groups classified according to responses to isoproterenol infusions. In the normal response group, seven patients were improved, three did not change, and none deteriorated. No patient died in the normal response group. However, in the low response group, only one patient improved, six did not change, and eight deteriorated. Six of the deteriorated patients died: three due to heart failure; two due to arrhythmias; and one died suddenly of an unknown cause. The total mortality rate during the present study was 20%.

Discussion

The prognosis of patients with DCM is reportedly poor. The average yearly mortality rate of DCM was about 10%[3,4]. However, a recent study revealed that a considerable number of DCM patients improved or, at least showed no change[7]. In the present study, surprisingly, 17 patients (68%) improved or did not change. One reason for such favorable prognoses is that our patients with DCM could be diagnosed at relatively early stages due to recent advances in echocardiography. Another reason is that our observation period was at most 21 months, which is not enough to induce the conclusion. Some patients who did not change during this observation period may be deteriorated subsequently.

Numerous studies have been performed to predict the outc ome of DCM. Factors predictive of DCM's outcome reportedly include age, sex, duration of symptoms, history of alcohol consumption or hypertension; abnormal cardiothoracic ratio; left ventricular end-diastolic pressure and volume, cardiac index, ejection fraction in cardiac catheterization; left ventricular end-diastolic dimension and fractional shortening on echocardiography; atrial fibrillation, ventricular arrhythmias and left ventricular conduction delay on electrocardiogram; and cell diameter and percent fibrosis in endomyocardial biopsy[4~11]. But none of these factors has been generally accepted. Fuster et al[3] followed up 104 patients with DCM and showed that cardiothoracic ratios on chest radiography and the cardiac index were highly predictive of the clinical course. Their study suggested the prognostic importance of left ventricular dimension and contractility at rest. However, a recentstudy showed improvement among some cases who had severely depressed contractility of their left ventricles at their first admission[4]. Another study refuted such prognostic efficiency of left ventricular dimensions[5]. In the present study, four of eight patients with markedly dilated left ventricles (LVDd>70 mm) deteriorated, three remained unchanged, and one improved. Two of 10 patients with mildly dilated left ventricles deteriorated, five remained unchanged, and three improved. This finding indicates that some patients' conditions may deteriorate, even though their cardiac dimen sions are not so large. This suggests that it is difficult to determine the prognosis using cardiac evaluations only in the resting condition. Evaluations during exercise are thought to be necessary. However, patients with DCM are at high risk during exercise stress tests, since fatal ar rhythmias can often occur during such exercise and heart failure might become more severe after exercise.

In our institute, a low dose isoproterenol infusion test has become an accepted stress test for high risk patients[12,13]. Isoproterenol is the most active sympathomimetic amines which act

nearly exclusively on β receptors. It has such strongly positive inotropic and chrono tropic effects that it increases myocardial oxygen consumption. It has therefore been used for diagnosing ischemic heart disease[12,13]. The main advantage of the low dose isoproterenol stress test is its safety.[14,15] Hemodynamic parameters return to pre-infusion levels one or two min after the drug is discontinued. Another advantage is that clear echocardiographic images can be obtained and cardiac function can be monitored during the stress test. We have shown that left ventricular response to isoproterenol can determine the prognosis of DCM. FS, one of the parameters of the ejection phase, is dependent on afterload. However, since there were no significant differences in left ventricular dimensions or blood pressures between the two groups, we have discussed left ventricular response according to FS.

Bristow et al. advanced a hypothesis that catecholamine sensitivity and β-adrenoreceptor density were decreased in the failing human heart[16,17]. The mechanism was thought to be that the levels of circulating catecholamine in the patients with symptomatic congestive heart failure were sig nificantly higher than those in normal controls, and that exposure to elevated levels of antagonists resulted in decreases of the total numbers of receptors. A depressed left ventricular response to isoproterenol might be partially due to "down-regulated" β receptors.

The prognostic variations in DCM are thought to be partially related to diverse etiologies. The etiology of DCM remains unknown, but current knowledge suggests that no single etiological agent will emerge, and that other multiple factors are probably concerned with this disease. Possible etiologies include metabolic defects[18], toxins[19], microvascular spasm[20], myocarditis[21], immunological disturbances and disturbances of adrenergic receptors. Several studies have shown prognostic significance of etiologies. One study suggested that alcohol-associated heart failure had a favorable prognosis, while peripartum cardiomyopathy patients may have the greatest one-year mortality[9,10]. In the present study, the prognosis of patients who had histories of relatively large alcohol consumption or influenza-like symptoms immediately prior to the development of cardiac symptoms was favorable. Patients without any etiological characteristics tended to have relatively poor prognosis. Therefore, the etiology of DCM may have prognostic significance. In the present study, information concerning the etiological contribution in DCM could not be obtained.

Medications are one of major factors influencing DCM patients' prognosis. In the present study, the main treatment for DCM patients consisted of diuretics and digitalis to reduce cardiac preload and to enhance cardiac contractility. Their doses were adjusted to the patients' changing conditions. Although drugs which reduce cardiac afterload are reportedly effective in the treatment of congestive heart failure[22~24], all but one patient did not receive them because hypotension was present or because their congestive heart failure was controlled only by diuretics and digitalis. Anticoagulation therapy was used in cases at risk of developing embolic disease. Other treatment such as immunosuppressive therapy or β-adrenergic blockade was not used for the patients in the present study, because their therapeutic efficacy has not been established. All patients were treated in our hospital or affliated hospitals; therefore, differences in therapy are not thought to influence their prognosis to an appreciable extent.

In summary, the prognostic value of isoproterenol was assessed in patients with DCM. Compared to patients in the normal response group, those in the low response group had poor prognoses. During the 21 months follow-up period, left ventricular responses to isoproterenol were predictive of prognoses.

要　約

拡張型心筋症におけるイソプロテレノール負荷試験の予後的意義

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拡張型心筋症症例 25 例(男 17 例，女 8 例)に isoproterenol 負荷を行い，左室機能の反応性と予後との関係を検討した．

本剤 0.02 μg/kg/min 注入による左室機能の反応性により，症例を，左室短縮率 (FS) が 10% 以上増加した反応群 (10 例) それ未満の反応低下群(15 例)に分類し，心エコー図法にて平均21ヵ月(4～40ヵ月)経過を追求した．経過を通じ，反応群では悪化0例，不変3例，改善7例であったが，反応低下群では悪化8例(死亡6例)，不変6例，改善1例で，反応群と比較して予後不良であった．

以上より，拡張型心筋症の予後判定に isoproterenol 負荷試験が有用であると考えられた．

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