Prognosis of Dilated Cardiomyopathy: From a Retrospective to a Prospective Study Employing Multivariate Analysis

SADAMASA OGASAWARA, M.D., MORIE SEKIGUCHI, M.D., MICHIAKI HIROE, M.D.
TSUTOMU KOMAZAWA, M.D.*, YUKO KAWAI, M.D., NAOYA FUJITA, M.D.
KENJI NAKAMURA, M.D., HIROSHI KASANUKI, M.D.*, ETSUKO TANAKA, M.D.
KENJI KOBAYASHI, M.D., MAKOTO OHTA, M.D.
AND KOSHICHIRO HIROSAWA, M.D.

To determine the prognostic factors of dilated cardiomyopathy (DCM), a retrospective long-term investigation of 111 patients seen between 1967 and 1983 was carried out. Fifty-four deaths were divided into 3 subgroups: (1): sudden death ($n = 6$); (2): sudden death on the basis of heart failure ($n = 17$); (3): refractory heart failure death ($n = 31$). Multivariate analysis was employed to ascertain the prognostic score, which was constructed from the grading of the New York Heart Association functional classification, the cardiothoracic ratio, electrocardiographic findings and cardiac function. Individual variables were indicated on the first (I) and second (II) principal component axes. The mean center points for the death modes were as follows: (1): $I = -0.4$, $II = +0.8$, (2): $I = +0.7$, $II = +1.1$, (3): $I = +1.4$, $II = -0.8$. Surviving cases ($n = 57$) showed $I = -0.6$, $II = +0.1$. Forty-one cases examined during 1984–1985 were analyzed to evaluate the prognostic efficacy of this score. Fourteen of 17 cases (82%) located in the refractory heart failure death group died within one year after determination of the prognosis, showing thereby that the prognostic determination by multivariate analysis is effective.

THE prognosis of dilated cardiomyopathy (DCM) is usually very poor due to the development of refractory congestive heart failure and grave arrhythmias.^{1–8} Because the cause of death is not uniform, it is advantageous to perform analytical studies to determine prognosis by etiology. Few reports of such studies have appeared to date in the literature.^{1–8} Since we have

had 24 years' experience^{9–18} in analyzing endomyocardial biopsy findings and our trial studies have proved useful for assessment of the prognosis of patients with DCM^{1,2,16,18} we constructed a prognostic score with the use of multivariate analysis and evaluated its use as an indicator of one-year survival in DCM patients.

MATERIALS AND METHODS

The subjects of this study consisted of 152 patients with DCM who were admitted to The Heart Institute of Japan between 1967 and 1985. These included 111 patients whose records were

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*The Heart Institute of Japan, Tokyo Women's Medical College and *Institute of Statistical Mathematics, Tokyo, Japan*

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Mailing address: Morie Sekiguchi, M.D., The Heart Institute of Japan, Tokyo Womens's Medical College, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan

TABLE I COMPARISON OF ELECTROCARDIOGRAPHIC CHANGES IN PATIENTS WITH DILATED CARDIOMYOPATHY

	Surviving group (n = 57)	Death group (n = 54)	p-value
Atrial arrhythmias	8	21	< 0.05
Left axis deviation	9	21	< 0.05
Prolongation of QRS interval	9	27	< 0.001
Low voltage	5	14	< 0.001
High grade ventricular arrhythmias	6	23	< 0.001

Atrial arrhythmias, left axis deviation, prolongation of QRS interval, low voltage and high grade ventricular arrhythmias were more frequently observed in the death cases.

subjected to a retrospective analysis to make the prognostic score (91 males and 20 females; age 40 ± 13 years (mean $\pm$ S.D.)) and 41 cases subjected to a prospective analysis to confirm the efficacy of the prognostic score (35 males and 6 females; age 42 ± 11 years). The follow-up period ranged from 3 months to 15 years (mean: 51 ± 30 months).

Seventy of 152 patients died of cardiac events during the follow-up period. Deaths were divided into 3 subgroups according to the manner of death, defined as; group 1: sudden death (n = 7), group 2: sudden death on the basis of congestive heart failure (n = 18), group 3: severe refractory heart failure death (n = 45).^{1,2}

A routine clinical analysis, employing history taking, chest roentgenogram, electrocardiography (ECG), continuous 24-hour ambulatory ECG recordings, using a portable cassette tape recorder (Holter monitor), M mode and two-dimensional echocardiographic studies, cardiac catheterization, left ventriculography and right ventricular endomyocardial biopsy were carried out and findings from the surviving group and the three death groups were compared.

Clinical criteria¹⁹: The diagnosis of DCM was based on the WHO/ISFC definition. Right ventricular endomyocardial biopsy was performed in all cases.

The severity of ventricular arrhythmia was graded according to the method of Ryne et al²⁰ in ambulatory 24-hour electrocardiographic recordings. High grade ventricular arrhythmias indicated grade 3 or higher.

Echocardiographic criteria: Percentage of shortening of left ventricular diameter was calculated using the formula; % shortening = (end-diastolic diameter – end-systolic diameter) / end-diastolic diameter $\times$ 100.

Hemodynamic assessment: Hemodynamic

measurements included left ventricular end-diastolic pressure (LVEDP), cardiac index (CI), left ventriculography and coronary arteriography. CI was determined by the thermodilution method. Left ventriculography was performed in the 30° right anterior oblique position, and left ventricular volume and ejection fraction were determined by the arealength method.²¹ Coronary arteriograms were obtained using Judkins method. There were no patients with stenosis of more than 50% of the luminal diameter in the major coronary arteries.

Right ventricular endomyocardial biopsy evaluation^{15–17}: A histopathological contractility failure index (HCFI)¹⁶ was constructed in order to assess the severity of the contractility failure of the left ventricle. The HCFI was based on light microscopical findings; i.e., fragmentation of muscle bundles, degeneration and myocytolysis of myocytes and interstitial fibrosis.

Multivariate analysis^{22–23}: Categorical principal component analysis (Hayashi's quantification theory type III)²² was employed as the prognostic score of DCM.

Treatment: Conventional medical therapy including bed rest, salt restriction, digitalis (148 patients), diuretics (150 patients), vasodilators (86 patients) and anti-arrhythmic drugs (84 patients) was applied.

Statistics: Each prognostic factors evaluated by Student's t-test or the Chi-square test. Data were presented as the mean value $\pm$ SEM.

RESULTS

1. Retrospective study

(1) Survival rate

The survival rate after the onset of subjective symptoms was 53% in the 5-year group and 22% in the 10-year group.

The severity of ventricular arrhythmia

Fig.1. Comparison of premature ventricular beats in patients with dilated cardiomyopathy determined by Holter monitoring.

The number of patients in each group of Ryne and Lown's classification²⁰ is shown. Block shading indicates death cases. In 44 of a total of 52 patients (81%), high grade ventricular arrhythmias were identified and mortality was 36%.

(2) Changes of the cardiothoracic ratio (CTR)

Changes in the CTR during the course of the disease were analyzed. The CTR at the first examination (A) and that seen shortly before the death of the patients (B) were compared. In group 1, there were no significant changes in CTR (A; 55.4 ± 1.3 , B; 54 ± 0.3 , $n = 6$). In group 3, the CTR was higher just before death of the patients than at the first examination (A; 60.6 ± 1.6 , B; 68.3 ± 0.8 , $p < 0.001$, $n = 31$). In contrast, the surviving cases showed a lower CTR than that seen at the start of the study (A; 59.3 ± 1.4 , B; 54.4 ± 1.0 , $p < 0.001$, $n = 57$).

(3) Electrocardiographic analysis

Comparison of ECG changes between the surviving and the death cases showed that atrial arrhythmias, left axis deviation, prolongation of the QRS interval, low voltage and high grade ventricular arrhythmias were more frequently observed in those who died than those who survived

Fig.2. The sum total of premature ventricular beats per 24 hours obtained by Holter monitoring.

There were more premature ventricular beats in the non survivors (5564 ± 1151) than in the survivors (837 ± 226). Values are mean $\pm$ SEM.

(Table I). A 24-hour ambulatory electrocardiographic study was performed in 52 patients (Fig. 1). Grades 0, 1 and 2 arrhythmias were present in only 8 of 52 cases, and all of them were surviving (mortality 36%). In 44 of 52 cases, high grade arrhythmias were identified.

A comparison of the total number of ventricular arrhythmias within 24 hours was performed between the surviving and death groups revealed that they were more frequent in those who died (5564 ± 1151) than in those who survived (837 ± 226) (Fig. 2). However, the mode of death did not differ with regard to the type and frequency of the ventricular arrhythmias.

(4) Echocardiographic analysis

Left ventricular end-diastolic diameter (LVDd), left atrial diameter (LAD) and percentage shortening of the left ventricular diameter (%FS) were compared between the survivors ($n = 34$) and the non survivors ($n = 19$). LVDd was greater in the non-surviving (43.4 ± 0.9

TABLE II PROGNOSTIC SCORE THROUGH MULTIVARIATE ANALYSIS^{22,23}
(SEE TEXT FOR AN EXPLANATION)

The First Principal Component Axis (I)			The Second Principal Component Axis (II)		
Item	Category	Score	Item	Category	Score
Supraventricular arrhythmia	(-)	-0.09	Supraventricular arrhythmia	(-)	-0.19
	(+)	+0.14		(+)	+0.29
Prolongation of QRS interval	(-)	-0.18	Low voltage	(-)	-0.02
	(+)	+0.29		(+)	+0.18
Low voltage	(-)	-0.06	Left axis deviation	(-)	+0.12
	(+)	+0.48		(+)	-0.47
Left axis deviation	(-)	-0.06	High grade ventricular arrhythmia	(-)	+0.11
	(+)	+0.22		(+)	-0.23
High grade ventricular arrhythmia	(-)	-0.05	NYHA functional classification	I or II	-0.07
	(+)	+0.11		III	+0.98
NYHA functional classification	I or II	-0.19		IV	-0.54
	III	+0.21	CTR (%)	< 55	-0.41
	IV	+0.41		55 ≤, < 65	+0.62
CTR (%)	< 55	-0.26		65 ≤	-0.53
	55 ≤, < 65	-0.01			
	65 ≤	+0.39			
LVEDP (mmHg)	< 18	-0.16			
	18 ≤	+0.17			
EF (%)	27 ≤	-0.17			
	< 27	+0.19			

Nine items are listed for the first principal component axis, and 6 items for the second principal component axis. NYHA class = New York Heart Association functional classification; CTR = cardiothoracic ratio; LVEDP = left ventricular end-diastolic pressure; EF = ejection fraction.

mm/m²) than in the survivors (35.9 ± 0.8 mm/m²) (p < 0.01), LVDs were greater in the non survivors (39.8 ± 0.8 mm/m²) than in the survivors (29.8 ± 0.9 mm/m²) (p < 0.01), %FS was lower in the non survivors (0.17 ± 0.11) than in survivors (0.99 ± 0.11) (p < 0.01), and LAD had increased more in those who died (26.3 ± 1.1 mm/m²) than in the survivors (19.6 ± 0.8 mm/m²) (p < 0.01).

(5) Cardiac function observed by cardiac catheterization and angiography

LVEDP, CI and ejection fraction (EF) in the two groups were compared. LVEDP was higher in the non survivors (22.1 ± 1.3 mmHg) than in the survivors (16.7 ± 1.2 mmHg) (p < 0.005), EF was lower among those who died (24.1 ± 1.6%) than in the surviving group (31.5 ± 1.8%) (p < 0.01), and CI was lower in those who died

(1.49 ± 0.09 L/min/m²) than in the survivors (2.46 ± 0.09 L/min/m²) (p < 0.005).

The 5-year survival rate in the group with LVEDP of less than 18 mmHg (n = 50) was 42% and in the group with 18 mmHg and above, it (n = 56) was 11% (p < 0.05). In the group with EF of less than 27% (n = 38), the survival rate was 10% and in the group with 18 mmHg and above, it (n = 40) was 42%.

(6) Histopathological contractility failure index

HCFI was higher in the non survivors (3.5 ± 0.01) than in the survivors (3.0 ± 0.2) (p < 0.05).

(7) A prognostic score of DCM through multivariate analysis

For the categorical principal component analysis, nine items were selected from those described

Fig. 3. Prognosis of dilated cardiomyopathy determined by multivariate analysis.^{22,23}

The first principal component axis (I) corresponds to two poles, i.e., surviving group on the left and death group on the right. The second principal component axis (II) shows the manner of death, i.e., sudden death and refractory heart failure death. Patients in the surviving group and the 3 death groups are plotted in two-dimensional space. ○ = surviving (n = 41), ▲ = sudden death (n = 3), ⊙ = sudden death on the basis of congestive heart failure (n = 8), ● = severe refractory heart failure death (n = 14).

above. Each item was divided into 2 or 3 categories. Outside variables were calculated for each category (Table II). Sixty-six patients of individual variables were indicated on the first (I) and second (II) principal component axis as the prognostic score (Fig. 3).

The mean center points for the sudden death group (n = 3) were I: -3.51, II: -2.06, the sudden death on the basis of congestive heart failure group (n = 8), I: +6.91, II: +10.9, the severe refractory heart failure death group (n = 14), I: +1.4, II: -0.8 and the surviving group (n = 41), I: -0.6, II: +0.1.

2. Prospective study

To evaluate the prognostic score, the most recent 41 patients were analyzed for one-year survival (Fig. 4). Twenty-five patients survived, and one died suddenly, another died suddenly on the basis of congestive heart failure and 14 died of severe refractory heart failure within one year after calculating the prognostic score. The

Fig. 4. One-year prognosis of dilated cardiomyopathy according to the prognostic score. Fourteen of the severe refractory heart failure death cases were located on the area of severe refractory heart failure death in the two-dimensional space. Oval figure delimits the area of severe refractory heart failure death and was constructed from results in Fig. 3. ○ = surviving (n = 26), ▲ = sudden death (n = 1), ⊙ = sudden death on the basis of congestive heart failure (n = 1), ● = severe refractory heart failure death (n = 14), ← = an example case plotted by using the score of the items in Table II (see text for details).

14 death patients from the 17 severe refractory heart failure patients were located in the area of severe refractory heart failure death (group 3) on the first and second principal component axis.

Forty-five of 152 cases who deteriorated into class IV in spite of the treatment with vasodilators and/or with new inotropic agents (TA-064)²⁴ were analyzed. The six-month survival rate after the onset of class IV heart failure under maximal medical treatment was 43% and the 12 month-survival rate was 17% (Fig. 5).

DISCUSSION

In this study, 152 patients were divided into a retrospective study (n = 111) and a prospective study (n = 41) in order to prospect a prognostic score and to confirm the efficacy of the scoring system. Analysis of the prognosis of DCM¹⁻⁸ indicated that the direct cause seemed to be due to congestive heart failure grave arrhythmias and sudden death. In this study, 70 death patients

Fig.5. Cumulative survival rate in dilated cardiomyopathy (n = 45) from the onset of refractory heart failure.

The six-month survival rate after the onset of class IV heart failure of NYHA classification under vasodilators or new inotropic agents is 43% and the 12 month survival rate is 17%.

were divided into 3 subgroup, i.e., sudden death (n = 7), sudden death on the basis of heart failure (n = 18) and refractory heart failure death (n = 45). Analysis of the clinical course, revealed that some patients died during the course of clinical improvement, and others showed gradual worsening and eventual death. The factors that predicted death were not uniform. Our previous study^{1,2} revealed 11 factors that were highly predictive of the prognosis of DCM, i.e., NYHA III or IV; CTR on chest roentgenography, atrial arrhythmias, left axis deviation, prolongation of QRS interval, low voltage, high grade ventricular arrhythmias, HCFI, LVEDP, EF and CI. We constructed prognostic index of DCM² on the basis of these factors, but it was not significantly objective. In this study, the prognostic score was constructed using multivariate analysis^{22,23} and it was shown to be a useful prognostic indicator. The prognostic score also showed that the separation of the manner of death into the first and second principal component axes is possible.

In the prospective study, 41 cases were analyzed for one-year survival to evaluate the predictive efficacy of this score (Fig. 4). For ex-

ample, calculation of the prognostic score is given. A 57-year-old male was discharged from our hospital. At discharge, his clinical data were: New York Heart Association functional class III, CTR of 69%, ECG of atrial fibrillation, no prolongation of QRS interval, left axis deviation low voltage and high grade ventricular arrhythmias, LVEDP of 24 mmHg and EF of 16%. The total score of the first principal component axis (I) was calculated as follows:

$$\begin{aligned} \text{(I)} &= +0.41 + 0.39 + 0.14 - 0.18 + 0.22 \\ &= +0.48 + 0.11 + 0.17 + 0.19 \\ &= +1.93 \end{aligned}$$

The total score of the second principal component axis (II) was calculated in the same manner as follows:

$$\begin{aligned} \text{(II)} &= -0.54 - 0.53 + 0.29 + 0.18 - 0.47 \\ &= -0.23 \\ &= -1.30 \end{aligned}$$

The position in the scatter diagram of category in item of this patient (prognostic score) is shown in two-dimensional space (arrow in Fig. 4). The patient died of refractory heart failure one month after discharge. Fourteen of 17 patients located on the refractory heart failure death area died within one year after determining the prognostic

score because of refractory heart failure. The prognostic score, therefore, proved to be highly predictive of one-year survival.

Fuster et al.⁸ also pointed out four factors that were independently and significantly predictive of the clinical course, i.e., age, CTR, CI, and LVEDP. In this study, the age of the patients did not affect the prognosis of DCM.

After 1977, vasodilator drugs or new inotropic agents, for example, captoril, prazosin and TA-064²⁴ were routinely used for patients with refractory heart failure whose clinical symptoms could not be improved beyond class III or IV of NYHA functional classification despite the administration of digitalis and diuretics. It has been proved that once patients deteriorate into refractory heart failure, the prognosis is extremely poor (Fig. 5), and cardiac transplantation²⁵ is indicated for such patients. The prognostic score, therefore, seems to be applicable for selection of the recipients of cardiac transplantation²⁵ in patients with DCM.

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