Original Article

Prediction of Prognosis of Patients with Idiopathic Dilated Cardiomyopathy: A Comparison of Echocardiography with Cardiac Catheterization

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The prognostic values of indices obtained by M-mode and two-dimensional echocardiography (Echo) and by cardiac catheterization (Cathe) were assessed in patients with idiopathic dilated cardiomyopathy. Fifty-one patients with this disorder (38 males and 13 females) were studied for an average of 4.2 years. Of those, 24 died of cardiac causes during follow-up. The overall 5-year survival rate was 49%. Significant differences between the surviving patients and the patients who died were noted in the following indices measured by Cathe: left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic pressure (LVEDP), ejection fraction (EF), and the cardiac index (CI). The 5-year survival rate in patients with the following index values measured by Cathe at the initial examination were: LVEDV $\geqq$ 150 ml/M^2 — 29%; LVEDP $>$ 12 mmHg — 35%, EF $<$ 30% — 21%, and CI $<$ 3.0 L/min/M^2 — 29%. In contrast, the 5-year survival rate in patients with the following parameter values measured by Echo were: left ventricular end-diastolic dimension $\geqq$ 45 mm/M^2 — 16%; left atrial dimension $\geqq$ 25 mm/M^2 — 12%; ejection fraction $<$ 30% — 31%; and a relative wall thickness (a ratio of left ventricular posterior wall thickness to left ventricular end-diastolic dimension) $\leqq$ 0.12 — 9%. In assessing the cumulative survival rate, the indices provided by Echo revealed similar values when compared with those obtained by Cathe. The relative wall thickness determined by Echo would be the most reliable parameter for forecasting the 5-year survival rate. In the majority of patients (22/24) who died during the observation period, the relative wall thickness gradually decreased to less than 0.12. Therefore, a relative wall thickness below 0.12 would be the most reliable index for detecting a poor prognosis case. It is concluded that echocardiographic observation of patients with idiopathic dilated cardiomyopathy can provide information useful not only in prognosis but also in assessing the effect of medical treatment.

Key Words: Idiopathic dilated cardiomyopathy, Echocardiography, Cardiac catheterization, Prognosis, Relative wall thickness

Idiopathic dilated cardiomyopathy is defined as "heart muscle disease of unknown cause", characterized by "dilatation of one or both ventricles and impairment of systolic function" (1). The diagnosis is made only after excluding the possibilities of structural heart disease and known causes of secondary heart muscle disorder (2). The prognosis is much poorer in idiopathic dilated cardiomyopathy than in other forms of idiopathic cardiomyopathy (3, 4). A rational diagnostic and therapeutic approach to any disease process depends upon understanding its natural history because the clinical course indicates where there is potential for therapeutic intervention to improve the prognosis

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(5). In addition, knowing the disease's natural history would be important in assessing therapy and developing appropriate treatment.

The purpose of this study is to determine the disease's natural history and any signs by which to predict the probability of survival in patients with idiopathic dilated cardiomyopathy. In this study, we compared the prognostic values of echocardiography and cardiac catheterization. The present study followed the course of 51 patients with idiopathic dilated cardiomyopathy who were observed in the Department of Cardiology at the Jichi Medical School.

METHODS

Study patients. The fifty-one patients (38 males and 13 females) admitted to this study had been diagnosed as having idiopathic dilated cardiomyopathy according to the definition and standards of the WHO/ISFC Task Force (1). Their ages were 32 to 77 years, with a mean of 55 years.

Methods. All 51 patients underwent echocardiography. 32 of these also received cardiac catheterization; their coronary arteriograms were normal. On the other hand, coronary artery disease was considered unlikely in the other 19 patients because of age, history, symptom, ECG findings and two-dimensional echocardiographic findings. Furthermore, none of the 51 patients abused alcohol, had history of definite hypertension, diabetes mellitus, or any other underlying systemic disease. In the absence of any other possible cause, this condition can be defined as "idiopathic dilated cardiomyopathy". Patients were observed for periods ranging from 4 months to 9 years (mean of 4.2 years) from the time of the first echocardiographic study.

Echocardiograms were recorded annually except in special cases. As shown in Fig. 1, two-dimensional echocardiography was used with M-mode echocardiography to select the best possible sites for measuring internal cardiac dimensions. Those sites were recorded, and as far as possible, echocardiography was repeated at those sites during follow-up. The echocardiographic apparatus used were Toshiba models SSH-11A and SSH-40A. The following parameters were recorded: left ventricular end-diastolic dimension (mm/M^2) and left ventricular end-systolic dimension (mm/M^2), aortic dimension (mm/M^2), and left atrial dimension (mm/M^2). These parameters were corrected against the body surface area. Additional observations included relative well thickness (a ratio of the left ventricular posterior wall thickness to the left ventricular end-diastolic dimension), and ejection fraction (%, calculated as the left ventricular end-diastolic volume — left ventricular end-systolic volume/left ventricular end-diastolic volume, where the left ventricular end-systolic volume and left ventricular end-diastolic volume were calculated by Teichholz Method (6) such that V (left ventricular volume) = $7D^3/2.4 + D$ (D = shorter axis)).

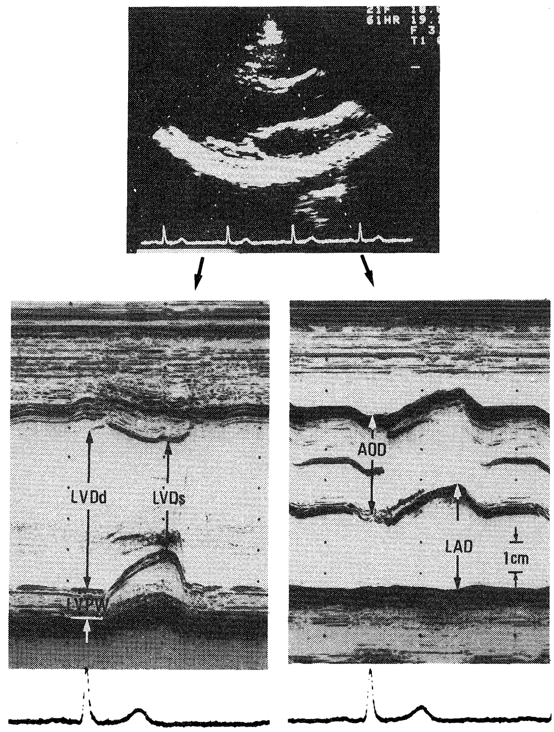

Fig. 1. Methods for measuring diameter. Diameters were measured by standard procedures as shown, using two-dimensional and M-mode echocardiograms.
Abbreviation; LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, LVPW: left ventricular posterior wall thickness, AoD: aortic dimension, LAD: left atrial dimension.

Cardiac catheterization and the first echocardiograph were conducted and the following parameters were calculated: cardiac index (L/min/M^2), ejection fraction (%), left ventricular end-diastolic pressure

(mmHg), and left ventricular end-diastolic volume (ml/M^2 corrected against the body surface area).

The parameters calculated from echocardiography and from cardiac catheterization were compared considering the surviving patients and those who died. "Survivors" were defined as patients who lived 3 years or longer after the first echocardiograph. "Deaths" referred to patients who died within 3 years of the same examination. Survival rate was estimated with the time of the first echocardiogram and cardiac catheterization defined as year 0 (initial date). Survival rate data were analyzed in relation to the various parameters derived from the two types of examinations. At their initial examination, we noted that these patients had received various treatments; some had received no therapy while others had been treated with digitalis or diuretics. After the first visit to our clinic, medical therapy with digitalis, diuretics, nitrates, or vasodilators was mainly prescribed, depending on the patient's cardiac condition and symptoms. If signs of cardiac failure were detected, β-stimulants were also administered. Antiarrhythmic agents and anticoagulants were prescribed as indicated.

Statistical analysis. The variables obtained by two-dimensional echocardiography and cardiac catheterization were compared between "Alive" and "Deceased" groups by unpaired Student's t-test (Fig. 3, Fig. 4). Survival rates were calculated by the life-table method. The statistical significance of differences between the survival curves was examined by generalized Wilcoxon test. The comparison among the cumulative survival curves in each index between echocardiographic and cardiac catheterization study was statistically analyzed by X square method. A probability value (p) of < 0.05 was considered statistically significant. Data were expressed as mean ± standard deviation.

RESULTS

Mortality rate.

Twenty-four of the 51 patients died within 4 months to 9 years after beginning the study. Sixteen of the 24 deaths resulted from cardiac failure while eight deaths were sudden and probably related to arrhythmia. As shown in Fig. 2, the 5-year survival rate in this group was 49%.

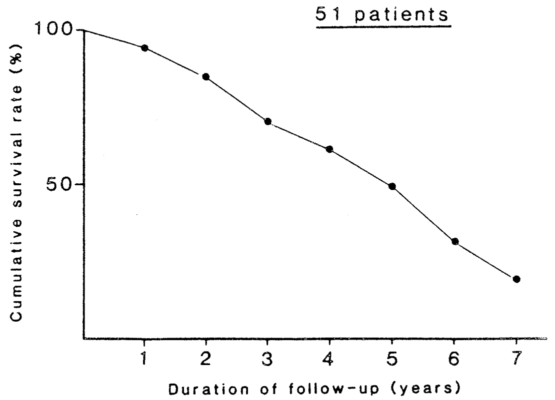

Fig. 2. Cumulative survival curve in 51 patients with idiopathic dilated cardiomyopathy. The 5-year survival rate in these patients was 49%.

Comparison of survivors with patients who died

With survival defined as living 3 years or longer beyond year 0 (the time of the first echocardiographic examination), 26 patients survived (18 of whom also underwent cardiac catheterization), while 14 (9 of whom also underwent cardiac catheterization) died within 3 years. Parameters calculated from echocardiography and cardiac catheterization were compared between the surviving patients and the patients who died, as described below.

Cardiac catheterization. Fig. 3 shows the mean value ± standard deviations of the various parameters in the survivors vs. those who died.

Left ventricular end-diastolic volume differed significantly ($p<0.01$) between the two groups of patients, being 155 ± 40 ml/M^2 in the survivors and 228 ± 63 ml/M^2 in those who died. Eight of the 9 patients who had a left ventricular end-diastolic volume of 150 ml/M^2 or less survived.

Left ventricular end-diastolic pressure also differed significantly ($p<0.05$) between the two groups with a mean of 15.2 ± 6.3 mmHg in the surviving patients and 21.8 ± 6.1 mmHg in those who died.

Ejection fraction also differed significantly ($p<0.001$) between the two groups, being 33.5 ± 7.2% in the survivors and 20.4 ± 6.4% in the patients who died. All 12 patients with an ejection fraction of 30% or higher survived.

The cardiac index differed significantly ($p<0.02$) between the two groups with a mean of 2.91 ± 0.67 L/min/M^2 in surviving patients and 2.21 ± 0.43

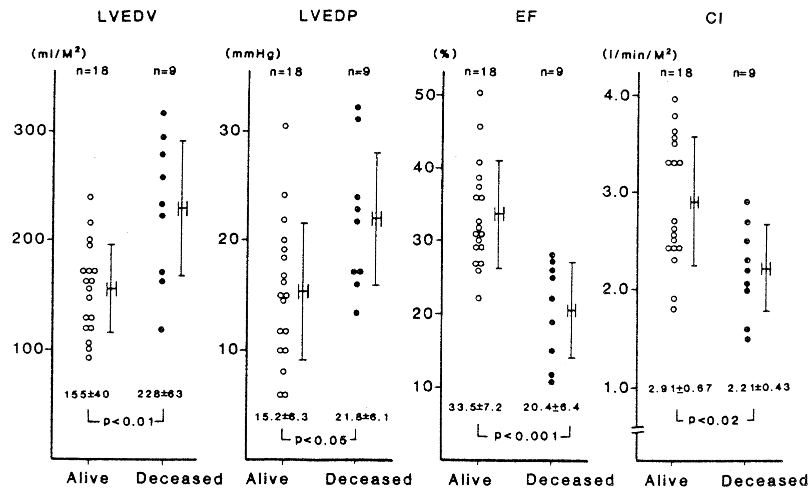

Fig. 3. Several indices provided by cardiac catheterization for predicting survival. Left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic pressure (LVEDP), ejection fraction (EF), and cardiac indices (CI) were used. There was a significant difference between the living and deceased groups in all these indices. The greatest differences were apparent in EF and LVEDV.

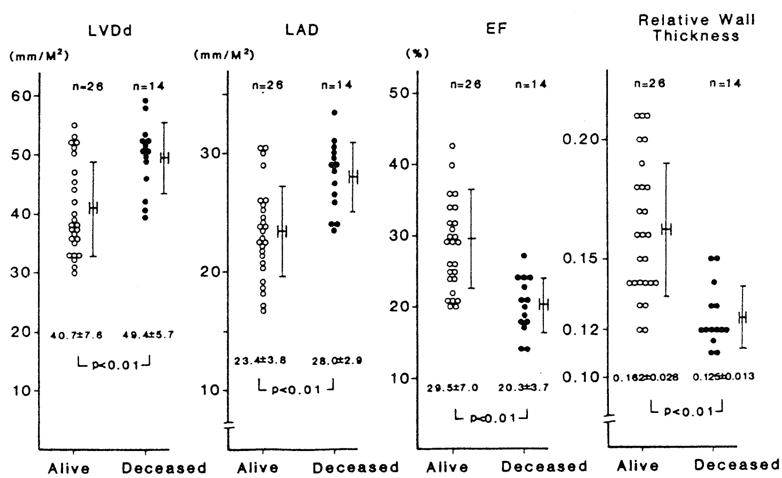

Fig. 4. Several indices provided by echocardiography for prediction of survival. LVDd, LAD, EF, and relative wall thickness (ratio between LVDd and LVPW) were used. There was a significant difference in all these indices between the two patient groups. The greatest difference was recognized in EF and in the relative wall thickness.

Abbreviations as in Figure 1.

L/min/M^2 in patients who died. All 8 patients with a cardiac index of 3.0 L/min/M^2 or more survived.

Echocardiography. Fig. 4 shows the mean values $\pm$ standard deviation of various parameters in the two groups.

The left ventricular end-diastolic dimension was significantly higher ($p<0.01$) in the patients who died (49.4 ± 5.7 mm/M^2) than in survivors (40.7 ± 7.6 mm/M^2).

The left atrial dimension also differed significantly between the two groups, being 23.4 ± 3.8 mm/M^2 in survivors vs. 28.0 ± 2.9 mm/M^2 in the deceased. None of the 13 patients with a left atrial dimension of 23 mm/M^2 or less died during the

study.

In addition, the ejection fraction differed significantly ($p<0.01$) between the two groups, being 29.5±7.0% in survivors vs. 20.3±3.7% in the deceased. None of the 12 patients with an ejection fraction of 29% or more died during the observation period.

The relative wall thickness differed significantly ($p<0.01$) between the two groups, measuring 0.16±0.03 in survivors vs. 0.13±0.01 in the deceased. None of the 14 patients with a relative wall thickness of 0.16 or more died during the observation period.

The aortic dimension was similar between the two groups, being 19.8±2.5 mm/M^2 in survivors and 20.0±2.0 mm/M^2 in the deceased.

5-year survival rate

Cardiac catheterization. Fig. 5 shows the 5-year survival rate from the time of cardiac catheterization. The 5-year survival rate was 83% in patients with a left ventricular end-diastolic volume less than 150 ml/M^2, and 29% in those with a value of 150 ml/M^2 or more, a significant difference ($p<0.01$).

The rate was 67% in patients with a left ventricular end-diastolic pressure of 12 mmHg or less, and 35% in those with values exceeding 12 mmHg, a significant difference ($p<0.01$). The rate was 78% in patients with an ejection fraction of 30% or more, and 21% in those with a value less than 30% ($p<0.01$).

Finally, the 5-year survival rate was 83% in patients with a cardiac index of 3.0 L/min/M^2 or more, and 29% in those with a value less than 3.0 L/min/M^2, again a significant difference ($p<0.01$).

Echocardiography. Fig. 6 shows the 5-year survival rate from the time of the initial echocardiogram.

The 5-year survival rate differed significantly ($p<0.01$) in the left ventricular end-diastolic dimension with a rate of 75% for patients with a left ventricular end-diastolic dimension of less than 45 mm/M^2, and 16% in those with a dimension of 45 mm/M^2 or more.

The rate was 72% for patients with a left atrial dimension of less than 25mm/M^2, and 12% for those with a dimension of 25 mm/M^2 or more, a significant difference ($p<0.01$).

The rate was 78% for patients with an ejection fraction of 30% or more, and 31% for those with less than 30%, a significant difference ($p<0.01$).

The 5-year survival rate was 58% for patients with a relative wall thickness exceeding 0.12 vs. 9% for those with a measurement of 0.12 or less, a significant difference ($p<0.01$).

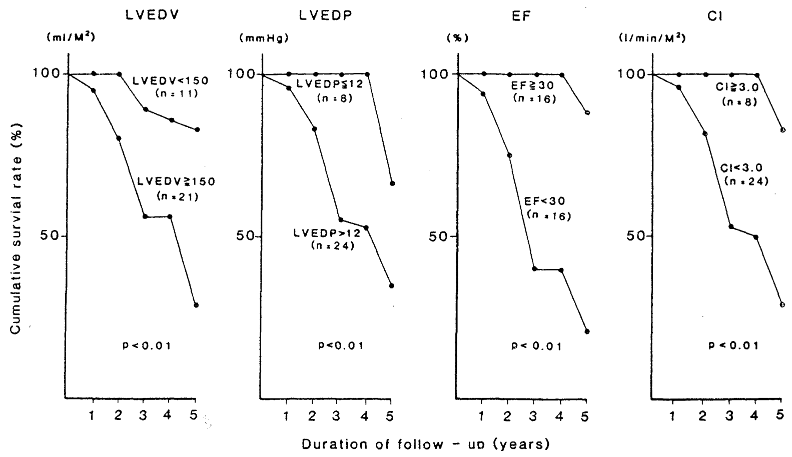

Fig. 5. Cumulative survival rate in each index measured by cardiac catheterization. The five-year survival rates in patients with LVEDV ≧ 150 ml/M^2, LVEDP > 12 mmHg, EF < 30%, and CI < 3.0 l/min/M^2 were 29%, 35%, 21% and 29%, respectively. Those with an EF lower than 30% showed the lowest 5-year survival rate.

Abbreviations as in Figure 1.

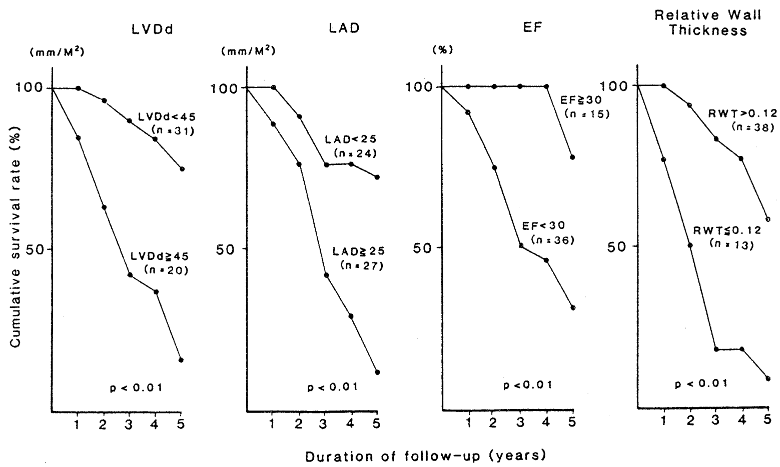

Fig. 6. Cumulative survival rate in each index measured by echocardiography. The five-year survival rates in patients with LVDd ≧ 45 mm/M^2, LAD ≧ 25 mm/M^2, EF < 30%, and relative wall thickness ≦ 0.12 were 16%, 12%, 31%, and 9%, respectively. The lowest survival rate was associated with a relative wall thickness less than 0.12.

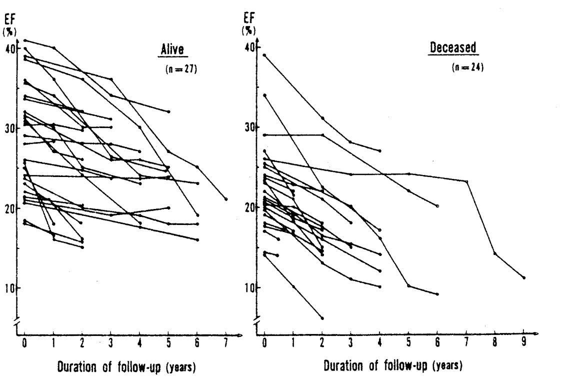

Fig. 7. Serial changes in EF measured by echocardiography. Surviving patients are indicated on the left, the deceased on the right. In both groups, the ejection fraction declined during the observation period. The deceased patients showed a steeper rate of decline. In addition, EF fell to less than 20% in many patients.

Abbreviations as in Figure 1.

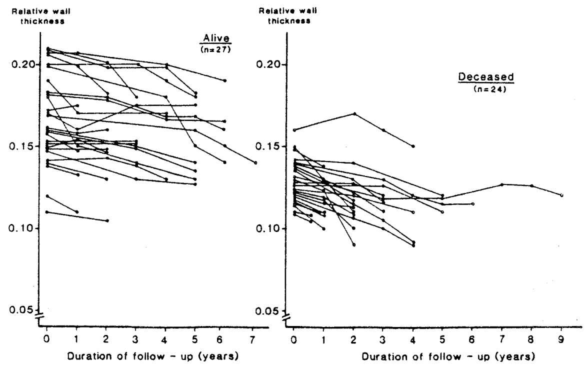

Fig. 8. Serial changes in relative wall thickness measured by echocardiography. Considerable differences were observed between the two patient groups. Only a few cases overlapped during the observation period. In the deceased group, almost all showed a progressive decrease in relative wall thickness to less than 0.12. The two surviving cases with a relative wall thickness lower than 0.12 are now compromised and bed fast.

Comparison of survival rate with the indices of cardiac catheterization and echocardiography. No statistical significance was identified among 5-year survival curves in each of the indices between cardiac catheterization and echocardiography. Furthermore, no statistical significance was recognized between the survival curves (5-year survival rate) in relative wall thickness ≦ 0.12 and the seven other indices (left ventricular end-diastolic volume ≧ 150 ml/M^2, left ventricular end-diastolic pressure > 12 mmHg, ejection fraction by catheterization < 30%, cardiac index < 3.0 L/min/M^2, left-ventricular end-diastolic dimension ≧ 45 mm/M^2, left atrial dimension ≧ 25 mm/M^2, and ejection fraction by echocardiography < 30%) (Fig. 5, Fig. 6).

However, in comparing in the 3-year survival rate, there were statistical significances between relative wall thickness ≦ 0.12 and the six other indices (left ventricular end-diastolic volume ≧ 150 ml/M^2, left ventricular end-diastolic pressure > 12

mmHg, cardiac index <3.0 L/min/M^2, left ventricular end-diastolic dimension $\geqq 45$ mm/M^2, left atrial dimension $\geqq 25$ mm/M^2 and ejection fraction by echocardiography $<30\%$) ($p<0.05$).

Progressive changes in echocardiographic parameters

Ejection fraction. Fig. 7 shows the progressive changes in ejection fraction in the 27 surviving patients and the 24 patients who died. Ejection fraction tended to decrease gradually in both groups but more rapidly in those who died than in the survivors. In addition, the ejection fraction decreased to 20% or less in only 11 (41%) of the 27 surviving patients, and in 20 (83%) of the 24 patients who died.

Relative wall thickness. Fig. 8 shows the progressive changes in relative wall thickness as measured by echocardiography. As with the ejection fraction, this parameter tended to decrease gradually in both patient groups. Ejection fraction changed similarly in many patients, whether they survived or died, but similar changes in relative wall thickness between survivors and those who died were infrequent, the value having decreased to a value of 0.12 or less in 22 (92%) of the 24 deceased patients, while only 2 of the 27 survivors showed a value of 0.12 or less (these 2 survivors were severely ill, classified in Stage IV of New York Heart Association (NYHA), and so were confined to bed).

DISCUSSION

Some year ago, Western reports showed a very poor long-term prognosis for idiopathic dilated cardiomyopathy; the 5-year survival rate was less than 40% (7, 8). However, recent reports show a slightly improved rate of about 50% (4). The survival rate in our patients was 49%. The Study Group of the Ministry of Health and Welfare of Japan for Idiopathic Cardiomyopathy demonstrated a slightly higher survival rate of 54.3% in 5 years, and 36.0% in 10 years. However, as mentioned in their report, more than 20% of their patients were excluded from the estimation of survival because the duration of follow-up was unknown. The survival rate of the excluded patients was low, suggesting that the overall survival rate may have been overestimated. However, survival has certainly improved in the last 10 years (3), partly due to improved therapy and better follow-up.

Prognosis depends on multiple factors. Failure of the cardiac pumping function secondary to the myocardial disturbance underlies idiopathic dilated cardiomyopathy, the prognosis of which depends on the progression of these functional and morphological abnormalities. Such alterations can be measured by echocardiography and serve as useful indicators of disease progression.

Major echocardiographic evidence of idiopathic dilated cardiomyopathy includes dilation of the left ventricular dimension, decreased ejection fraction, decreased contractility in the septum and the left ventricular posterior wall, decreased C/E amplitude in the mitral valve, increased A/E ratio, B-B' step formation, an increase in the mitral valve E point to ventricular septal separation, decreased percent fractional shortening, and increased left atrial dimension. Three of those factors have been reported helpful in evaluating disease and establishing a prognosis: percent fractional shortening, a measure of myocardial contractility, dilated left ventricular dimension, characteristic of idiopathic dilated cardiomyopathy, and a reduced thickness of the left ventricular wall secondary to the dilated left ventricular dimension (10-15).

The clinical characteristics and natural history of idiopathic dilated cardiomyopathy are well described (5, 7, 16-19), and Benjamin (20), Feild (21) and Das et al. (22) reported about relative left ventricular wall thickness at autopsy, mass/volume index and prognosis in relation to therapy, respectively. However there are few reports on its prognosis in relation to various echocardiographic parameters based on long-term follow-up. The present study compared such echocardiographic parameters with those obtained by cardiac catheterization.

Left ventricular end-diastolic volume, left ventricular end-diastolic pressure, ejection fraction, and cardiac index determined by cardiac catheterization were compared between the surviving patients and those who died. As shown in Fig. 3, these parameters differed significantly between the two groups. Significant differences were particularly marked in the ejection fraction and left ventricular end-diastolic volume.

Fuster et al. (7) followed patients for 6 years and reported a 6-year survival rate of 11% for patients

with a cardiac index of less than 3.0 $L/min/M^2$, 65% for those with a cardiac index of 3.0 $L/min/M^2$ or more, 13% for those with a left ventricular end-diastolic pressure of 20 mmHg or more, and 37% for those with a left ventricular end-diastolic pressure of less than 20 mmHg. The survival rate of our patients with a cardiac index of less than 3.0 $L/min/M^2$ was similar to that reported nongraphically, but in equivalent terms by Fuster, et al.

Many reports (8, 9, 23) have failed to show significant differences in left ventricular end-diastolic dimension, ejection fraction, and other echocardiographic parameters when comparisons were made simply between the patients who survived during follow-up and those who died. Our study, however, in the 3-year survival rate following the initial examination, clearly demonstrates a significant difference in the left ventricular end-diastolic dimension, left atrial dimension, ejection fraction, and relative wall thickness between the survivors and those who died. In this respect, ejection fraction and relative wall thickness were of particular importance.

In the indices by echocardiography, the most sensitive sign of an unfavourable clinical course was a relative wall thickness of 0.12 or less. Data on 5-year survival derived from the first echocardiographs indicated that echocardiography could reveal a poor prognosis patient more reliably than cardiac catheterization.

In comparing the indices measured by the above two methods, the two pairs of indices such as left ventricular end-diastolic volume vs. left ventricular end-diastolic dimension, and ejection fraction by cardiac catheterization vs. ejection fraction by echocardiography showed good correlation for predicting the clinical course of patients with idiopathic dilated cardiomyopathy. Thus, the non-invasive method (echocardiography) was also a good prognostic tool. However, the left ventricular end-diastolic pressure could not be measured by a non-invasive method. On the other hand, relative wall thickness could not be obtained by cardiac catheterization (invasive method) and was instead assessed by both morphological and hemodynamic features.

By comparing the prognostic value of the data derived from echocardiographic and catheterization study, no statistical significance was recognized among 5-year survival curves in each of the indices by above two methods. However, the 5-year survival rate of relative wall thickness $\leqq 0.12$ was the poorest among these indices and in assessing in 3-year survival rate, statistical significances were recognized between relative wall thickness $\leqq 0.12$ and six other indices. In addition, follow-up study by echocardiography revealed few overlapping cases between alive and deceased patients in the index of relative wall thickness. Therefore, we considered that it would be the most reliable index of these ones.

Progressive changes in ejection fraction and relative wall thickness in the surviving patients and those who died provided information useful in predicting the clinical course of idiopathic dilated cardiomyopathy. Relative wall thickness has been reported to provide diagnosis and prognostic data in patients with a broad variety of cardiac disorders (24). Then, we first used this index by echocardiography in follow-up study for the predicting the prognosis in patients with idiopathic dilated cardiomyopathy.

Relative wall thickneess (2W/R) directly represents myocardial stress against left ventricular load, expressed according to Laplace's equation as: stress = tension (PR)/myocardial cross section area (2W), where P = internal pressure, R = internal dimension, and W = wall thickness. Thus, stress increases as R increases, or as W decreases. If this relationship is applied to idiopathic dilated cardiomyopathy, R increases as the pre-load or after-load increases, while W seems to decrease if the wall is stretched as the left ventricular dimension dilates, or if there is progressive degeneration of the myocardium itself. As previously reported, in the case of dilated cardiomyopathy with decompensation, a further decrease in left ventricular wall thickness, further increase in left ventricular volume, and a further fall in ejection fraction are found. Despite an increased after-load, evidence of left ventricular wall hypertrophy is absent. This is particularly important in establishing the prognosis. A decreased wall thickness associated with a dilated left ventricular dimension may suggest a lack of a compensatory mechanism for the contraction failure (25).

In summary, the indices determined by cardiac catheterization were accurate predictors of a relatively good clinical course of idiopathic dilated

cardiomyopathy. On the other hand, as compared with the those of cardiac catheterization the echocardiographic indices were also good predictors of increased left ventricular decompensation; that is, they were particularly suitable to identifying poor prognosis patients.

CONCLUSION

The natural progression of idiopathic dilated cardiomyopathy was studied in 51 patients. The prognostic value of cardiac catheterization in predicting the clinical course was compared with that of echocardiography. Several parameters of cardiac catheterization were useful in establishing a prognosis. However, echocardiography can be repeated so that patients can be monitored over the long-term. Echocardiography seems to be helpful not only in making a prognosis, but also in evaluating the response to therapy.

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