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MORPHOLOGIC STUDIES

Functional and Histopathologic Correlation in Patients With Dilated Cardiomyopathy: An Integrated Evaluation by Multivariate Analysis

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To correlate left ventricular function and histologic features in patients with dilated cardiomyopathy, precise indexes of hemodynamics and semiquantitative histologic data were combined for multivariate analysis. Right endomyocardial biopsy was performed at the time of cardiac catheterization. Five hemodynamic indexes were used for functional assessment: 1) ejection fraction, 2) ratio of end-systolic stress to volume index, 3) end-diastolic stress, 4) time constant (T) of left ventricular pressure fall, and 5) end-systolic stress. Six histologic findings (disarray of myofibers, hypertrophy of myofibers, scarcity of myofibrils, nuclear changes of myofibers, vacuolization of myofibers and proliferation of collagen fibers) were graded from (−) to (4+). Each finding was assigned to category (−) or (+) according to the absence or presence of significant abnormality.

Ordinary statistical analysis revealed that, although ejection fraction was lower in category (+) for proliferation of collagen fibers, ratio of end-systolic to volume index was reduced for category (+) of hypertrophy of myofibers. A significant correlation was present between hypertrophy of myofibers and proliferation of collagen fibers by Spearman rank correlation. When principal component analysis was applied to the hemodynamic data, two principal components could be extracted. Fisher's discriminant analysis could clearly differentiate two categories (−) and (+) in the semiquantitative histologic finding of proliferation of collagen fibers. The analysis indicated that contractility was reduced with elevated afterload in that category (+). Thus, proliferation of collagen fibers may play a pivotal role in deteriorating contractility in patients with dilated cardiomyopathy.

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Dilated cardiomyopathy is characterized by a dilated ventricle and depressed myocardial contractility of unknown origin (1–3). The histologic characteristics of this disease are hypertrophy of myofibers, myofibrillar lysis, nuclear changes and vacuolization of myocardial fibers and interstitial fibrosis of the myocardium (4–7). On the assumption that there is a close correlation between ventricular function and myocardial morphologic findings, several investigators (8–13) have tried to correlate the function and anatomy of the heart. They have reported a simple relation between the histologic findings and a single index of contractility, such as ejection fraction. Recent progress in hemodynamic analysis allows more precise assessment of cardiac contractility than is afforded by a single use of ejection phase indexes that can be influenced by preload or afterload (14–17). Therefore, previous studies could not fully evaluate the complex integration of both aspects.

The purpose of this study was to clarify the relation between functional characteristics and morphologic findings by applying a recent hemodynamic approach and semiquantitative histologic analysis. We evaluated these correlations by means of multivariate analysis, a useful statistical method of comparing multiple events and determining principal factors, to find the hallmarks of reduced cardiac performance in dilated cardiomyopathy.

Methods

Study patients. Twenty-four patients (18 male and 6 female) with dilated cardiomyopathy and 25 normal control subjects (18 male and 7 female) who underwent diagnostic cardiac catheterization because of suspected dilated cardiomyopathy, a heart murmur or chest pain were evaluated after giving informed consent. The final diagnosis of dilated cardiomyopathy was made according to the report (3) of the World Health Organization/International Society and Fed-

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eration of Cardiology task force on the definition and classification of cardiomyopathies. Cardiac catheterization and endomyocardial biopsy were performed in the patients with dilated cardiomyopathy after vigorous medical treatment for 1 to 2 months. Twelve patients were mildly symptomatic (New York Heart Association functional class II) and 12 patients still had severe congestive heart failure (classes III to IV) at the time of cardiac catheterization.

Cardiac catheterization. The details of the catheterization procedure have been described elsewhere (16–19). Briefly, left heart catheterization was performed with a manometer-tipped angiocatheter. Left ventricular cineangiograms were recorded in a 30° right anterior oblique projection. Coronary cineangiography was performed by the Sones' technique. At the end of the catheterization procedure, endomyocardial biopsy was performed with a Konno-Sakakibara bioptome introduced through the right femoral vein in all patients with dilated cardiomyopathy. We obtained multiple biopsy specimens from the right side of the interventricular septum in every patient with dilated cardiomyopathy. Endomyocardial biopsy of the left ventricle could not be done in some cases because of the presence of mural thrombi and the data were analyzed for only right ventricular specimens.

Hemodynamic data. Five consecutive beats in patients with normal sinus rhythm and 10 consecutive beats in patients with atrial fibrillation were averaged for the determination of pressures and their derivatives. Left ventricular volumes were calculated by the area-length method of Dodge et al. (20) with normalization by body surface area to end-diastolic and end-systolic volume indexes, and ejection fraction was obtained with the standard formula. The time constant of the left ventricular pressure fall (time constant T) was obtained for the evaluation of left ventricular relaxation (21). Midwall circumferential stress (σ) was calculated at end-diastole and end-systole from the instantaneous left ventricular dimensions, wall thicknesses and pressures by the formula of Mirsky (22), $\sigma = PB/h(1 - h/2B - B^2/2A^2)$, where P is pressure, h is wall thickness and A and B are long and short radii to the midwall, respectively. End-diastolic stress (σed) and end-systolic stress (σes) were used for the assessment of preload and afterload, respectively. Because recent studies have suggested better methods than ejection fraction for evaluating cardiac contractility (14–17), we applied the ratio of end-systolic stress to end-systolic volume index (σes/ESVI) as an index of contractility in this study (14).

Endomyocardial biopsy. Multiple biopsy specimens were fixed in 10% formalin, dehydrated with a series of ethanol solutions and embedded in paraffin. From the paraffin blocks, sections about 4 μm thick were cut, stained with hematoxylin-eosin, elastic-van Gieson, Mallory-azan or periodic acid-Schiff and examined under a light microscope. The histopathologic features of the biopsy specimens were analyzed by one of us without clinical information. The following histopathologic findings were specifically examined in each biopsy specimen; disarray of myofibers, hypertrophy of myofibers, scarcity of myofibrils, nuclear changes, vacuolization including perinuclear changes and proliferation of collagen fibers (4). On the basis of the semiquantitative scoring system of histologic findings (see Appendix), we classified these findings into two categories: 1) category (−), no significant histologic changes, and 2) category (+), significant histologic changes.

Statistics. *1) Interrelations among histologic findings.* Relations among semiquantitative histologic findings were evaluated by the Spearman rank correlation. The significance of the correlation coefficients was determined with Student's t test. A probability (p) value of <0.05 was considered significant.

2) Relations between hemodynamic data and histologic findings. To correlate the hemodynamic indexes and the histologic findings, we used three steps in our statistical approach: a) Student's t test, b) principal component analysis, and c) Fisher's discriminant analysis.

a) Using five hemodynamic findings as statistical variables, we compared categories (−) and (+) for each semiquantitative histologic feature according to the scoring system using the unpaired Student's t test to find important factors of the statistical model.

b) To determine the contribution of each hemodynamic variable to cardiac performance, we applied principal component analysis to five hemodynamic indexes. To obtain the regression formula to regulate cardiac events in each principal component, we calculated and plotted principal scores in a two-dimensional framework, the first principal component on the abscissa and the second principal component on the ordinate.

c) *To differentiate category (−) from category (+) according to the semiquantitative scoring system,* we examined the scores obtained from the first and second principal components using Fisher's discriminant analysis.

Results

Hemodynamic data of patients with dilated cardiomyopathy (Table 1). Briefly, patients with dilated cardiomyopathy had relatively lower systolic pressures than did normal control subjects with similar end-diastolic pressures. The hemodynamic findings in dilated cardiomyopathy were low cardiac output and an enlarged and poorly contracting left ventricle, that is, high end-diastolic and end-systolic volumes with low ejection fraction. Although end-diastolic stress remained in the normal range, end-systolic stress was markedly elevated. The ratio of end-systolic stress to end-systolic volume index was significantly reduced. These findings indicated reduced contractile function and elevated afterload with normal preload in dilated cardiomyopathy. The

Table 1. Hemodynamic and Angiographic Data

Patient Group	Age (yr)	LVSP (mm Hg)	LVEDP (mm Hg)	EDVI (ml/m^2)	ESVI (ml/m^2)	CI (liters/min per m^2)	EF (%)	σ es/ESVI (g·m^2/cm^2 per ml)	T (ms)	σ ed (g/cm^2)	σ es (g/cm^2)
DCM	45	112	9	131*	88*	2.50*	35*	3.03*	62*	34	237*
(n = 24)	± 10	± 19	± 6	± 40	± 40	± 0.75	± 13	± 1.09	± 10	± 35	± 70
NC	41	121	9	69	24	3.28	66	6.32	34	25	148
(n = 25)	± 16	± 11	± 3	± 19	± 9	± 0.86	± 7	± 2.45	± 9	± 10	± 59

Values are mean ± SD. *$p < 0.001$. CI = cardiac index; DCM = dilated cardiomyopathy; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; NC = normal control; σ ed = end-diastolic stress; σ es = end-systolic stress; T = time constant of left ventricular pressure fall.

prolonged time constant T of left ventricular pressure fall indicated the presence of abnormal relaxation.

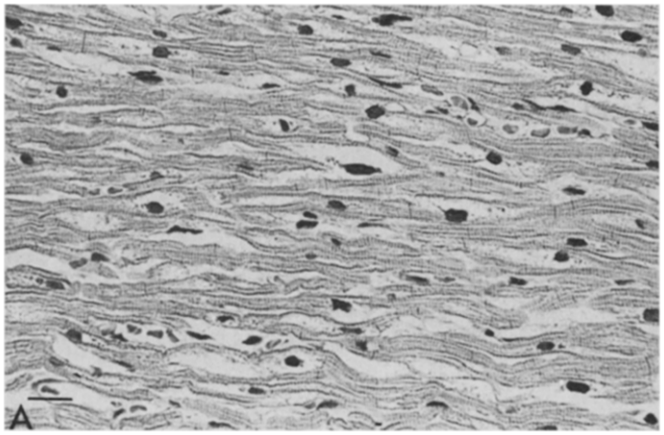
Histopathologic features in dilated cardiomyopathy (Table 2). The incidence of each semiquantitative histologic finding was as follows: disarray of myofibers, 12.5%; hypertrophy of myofibers, 33.3%; scarcity of myofibrils, 29.2%; nuclear changes, 66.7%; vacuolization, 25.0%; and proliferation of collagen fibers, 37.5%.

We compared each semiquantitative histologic finding between groups with mild (functional class II) and severe (classes III to IV) congestive heart failure using Fisher's exact test. With respect to proliferation of collagen fibers,

Table 2. Histologic Findings in 24 Cases of Dilated Cardiomyopathy

Patient No.	Age (yr) & Sex	NYHA Class	Disarray of MF	Hypertrophy of MF	Scarcity of Mf	Nuclear Changes	Vacuolization	Proliferation of Collagen Fibers
Group With Mild Congestive Heart Failure (class II)								
4	38M	II	3(+)	0(−)	1(−)	1(−)	1(−)	0(−)
5	31F	II	2(−)	0(−)	0(−)	0(−)	1(−)	0(−)
6	50F	II	1(−)	0(−)	1(−)	1(−)	1(−)	0(−)
7	55M	II	1(−)	0(−)	1(−)	1(−)	1(−)	1(−)
12	63M	II	2(−)	0(−)	1(−)	2(+)	1(−)	1(−)
14	48M	II	1(−)	0(−)	1(−)	2(+)	2(+)	1(−)
18	50M	II	2(−)	0(−)	1(−)	3(+)	2(+)	0(−)
19	57M	II	3(+)	0(−)	1(−)	3(+)	2(+)	2(+)
20	50M	II	1(−)	1(+)	1(−)	1(−)	1(−)	0(−)
22	45M	II	1(−)	0(−)	2(+)	2(+)	2(+)	0(−)
23	44M	II	2(−)	1(+)	2(+)	3(+)	1(−)	1(−)
24	35M	II	2(−)	1(+)	2(+)	3(+)	2(+)	2(+)
(+)/(−)			2/10	3/9	3/9	7/5	5/7	2/10
Group With Severe Congestive Heart Failure (classes III to IV)								
1	41M	III	3(+)	1(+)	2(+)	1(−)	1(−)	3(+)
2	42M	III	1(−)	3(+)	1(−)	1(−)	1(−)	2(+)
3	25F	IV	2(−)	2(+)	1(−)	3(+)	0(−)	2(+)
8	27M	IV	0(−)	0(−)	2(+)	3(+)	1(−)	2(+)
9	57F	III	2(−)	0(−)	1(−)	2(+)	1(−)	1(−)
10	51F	III	2(−)	0(−)	2(+)	2(+)	1(−)	1(−)
11	53M	III	2(−)	0(−)	1(−)	2(+)	1(−)	1(−)
13	58M	IV	1(−)	1(+)	1(−)	2(+)	1(−)	2(+)
15	49M	IV	2(−)	0(−)	1(−)	3(+)	2(+)	2(+)
16	41M	III	1(−)	0(−)	1(−)	3(+)	1(−)	1(−)
17	40F	IV	1(−)	2(+)	2(+)	1(−)	1(−)	3(+)
21	50M	III	2(−)	0(−)	1(−)	2(+)	1(−)	1(−)
(+)/(−)			1/11	5/7	4/8	9/3	1/11	7/5
NYHA class II vs. NYHA class III to IV			NS	NS	NS	NS	NS	$p < 0.05$

F = female; M = male; Mf = myofibrils; MF = myofibers; NYHA Class = New York Heart Association functional class; (+) = category (+); (−) = category (−).



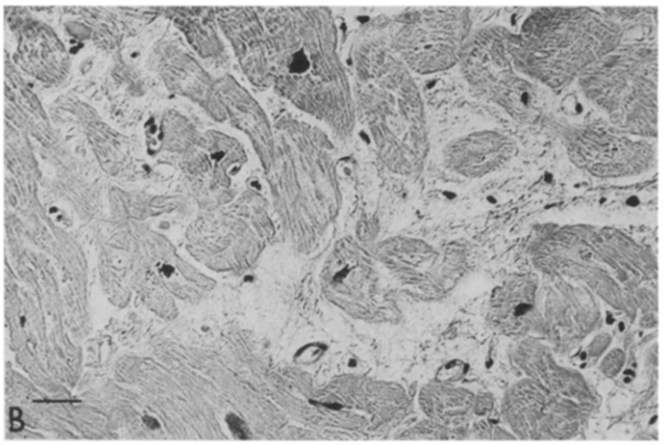


Figure 1. A, Patient 5. Light micrographs of biopsy specimens of dilated cardiomyopathy of a mildly symptomatic patient with class II congestive heart failure. This case is classified in category (−) of all semiquantitative findings. **B,** Patient 2 (class IV), a patient with typical findings of severe histologic changes, hypertrophy of myofibers [grade 3; category (+)] and proliferation of collagen fibers [grade 2; category (+)]. Hematoxylin-eosin stain; scale bar: 20 μm.

the incidence of category (+) was higher ($p < 0.05$) in patients with severe congestive heart failure than in those with mild failure. Typical histologic findings of mild (class II) and severe (classes III to IV) congestive heart failure are presented in Figure 1; hypertrophy of myofibers and proliferation of collagen fibers are seen in Figure 1B.

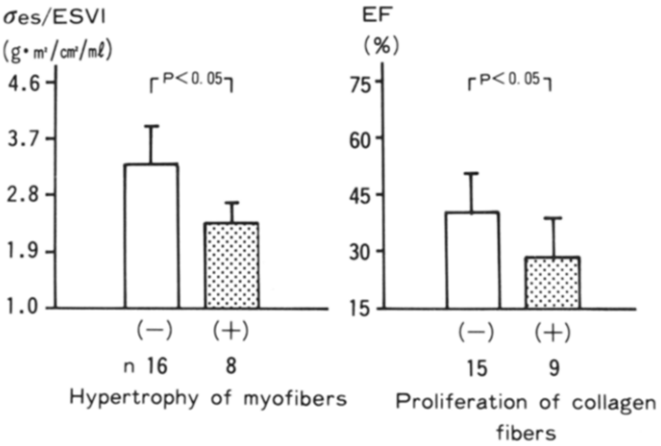


Figure 2. Depressed contractility in relation to semiquantitative histologic findings. The hemodynamic variables were compared between categories (−) and (+) of each histologic finding by Student's *t* test. The results showed a reduced end-systolic stress/end-systolic volume index ratio (σes/ESVI) [category (−): 3.35 ± 1.14 versus category (+): 2.39 ± 0.67 $g \cdot m^2/cm^2$ per ml, $p < 0.05$] and ejection fraction (EF) [category (−): 39.7 ± 11.4 versus category (+): 28.1 ± 11.6%, $p < 0.05$]. The data suggest that hypertrophy of myofibers and proliferation of collagen fibers may reduce cardiac contractility in dilated cardiomyopathy. n = number of cases.

Interrelations among individual histologic features (Table 3). The correlation coefficients suggested a close relation between the development of hypertrophy of myofibers and the proliferation of collagen fibers ($r = 0.55$, $p < 0.01$).

Relation between hemodynamic data and histologic features. 1) The ratio of end-systolic stress to end-systolic volume index was significantly low in patients with hypertrophy of myofibers. The ejection fraction was significantly decreased in patients with proliferation of collagen fibers. These results suggested that hypertrophy of myofibers and proliferation of collagen fibers are closely related to depressed contractility in dilated cardiomyopathy (Fig. 2).

2) Principal component analysis could extract two dominant principal components from five hemodynamic variables: ejection fraction and end-systolic stress. The contribution rate and coefficients (or weights) of the first and

Table 3. Matrix of Spearman Rank Correlations

	Hypertrophy of Myofibers	Scarcity of Myofibrils	Nuclear Changes	Vacuolization	Proliferation of Collagen Fibers
Disarray of myofibers	0.00	0.04	−0.27	0.07	0.23
Hypertrophy of myofibers		0.32	−0.25	−0.20	0.55*
Scarcity of myofibrils			0.07	0.05	0.26
Nuclear changes				0.40	0.00
Vacuolization					0.15

*$p < 0.01$.

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Table 4. Weights (factor loadings) From Principal Component Analysis of Five Hemodynamic Variables

	First Component	Second Component
EF	0.862	0.358
σ es/ESVI	0.429	0.856
T	−0.700	0.069
σ ed	−0.687	0.272
σ es	−0.764	0.577
Contribution rate (%)	49.4	25.5

Each principal component would be characterized by large weights, because variables with a large weight were highly correlated with individual principal components. Abbreviations as in Table 1.

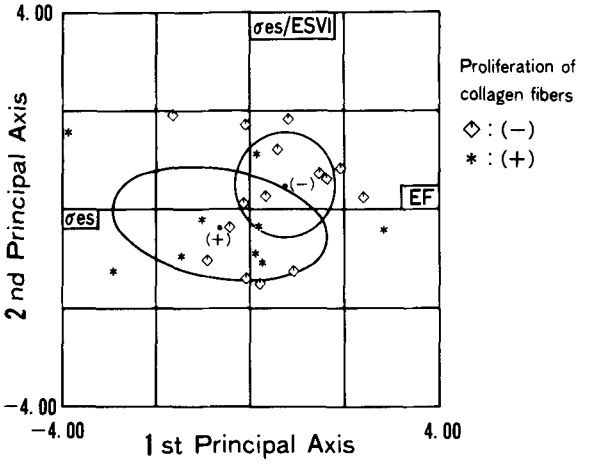

Figure 3. Fisher's discriminant analysis on contractility indexes and semiquantitative histologic findings. The **abscissa** represents the first principal component and the **ordinate** represents the second principal component of the discriminant analysis. For each principal axis, variables with a high contribution rate to the axis are shown in the **frames** (σes, EF, σes/ESVI). The **positive direction** on either the **abscissa** or the **ordinate** indicates better contractility. The **right upper area** represents good contractility and the **left lower area** reduced contractility. Both categories (−) and (+) can be clearly separated by this analysis; that is, category (−) is located in the **right upper quadrant** and category (+) in the **left lower quadrant.** These results suggest that cardiac contractility is depressed with elevated afterload in the category with higher grades for proliferation of collagen fibers by the semiquantitative scoring system, indicating more serious changes. Abbreviations as in Figure 2.

second principal components corresponding to the five variables are shown in Table 4. The first principal component contributed 49.4% of the total variance and played an important role in explaining the state of the five hemodynamic variables. The ejection fraction and the end-systolic stress had the two largest weights (0.862 and −0.764), indicating a stress-shortening relation.

The second principal component accounted for 25.5% of the total variance, and the ratio of end-systolic stress to end-systolic volume index had a large positive weight (0.856), reflecting contractility. We used the first and second principal components as indexes of contractility and applied Fisher's discriminant analysis.

3) The results of applying Fisher's discriminant analysis to the contractility indexes and semiquantitative histologic findings are shown in Figure 3. The confidence ellipsoids clearly separated the two categories, (−) and (+), of proliferation of collagen fibers. These results indicated a correlation among reduced contractility, elevated afterload and proliferation of collagen fibers in dilated cardiomyopathy.

Discussion

Dilated cardiomyopathy is defined as a disease in which a dilated ventricle with low ejection fraction results in congestive heart failure (1–3) and the histologic findings of the myocardium are characterized by hypertrophy of the myofibers, myofibrillar lysis, nuclear changes, vacuolization, collagen fiber proliferation or disarray of myofibers (4–7). Hemodynamic studies of this disease have proved that its natural history is very poor because of irreversibly progressing congestive heart failure (17,23). Endomyocardial biopsy has shown that interstitial fibrosis has a prognostic value (24). Because the progressive heart failure and the fibrosis seem to change in parallel, we considered that there might be some functional and morphologic correlation in this disease.

Several investigators (9–12) have reported a correlation between histologic findings on endomyocardial biopsy and hemodynamic data in dilated cardiomyopathy. Even though they evaluated histologic quantification such as percent fibrosis, percent volume of myofibrils and integrated light and electron microscopic scores, they used only a single contractility index such as ejection fraction. Because multiple events participate in the regulation of cardiac performance, it is not valid to compare a single hemodynamic index with the histologic findings. To obtain a precise assessment of the relations between hemodynamic and morphologic states of this disease, we designed a hybrid model with both functional and morphologic findings.

Advantage of multivariate analysis to integrate function and morphology. Multivariate analysis is a useful statistical method for analyzing a complex model in which multiple factors participate and it can provide a good analysis of the correlation of cardiac performance and semiquantitative histologic data. We examined five hemodynamic variables by principal component analysis (one form of multivariate analysis) combining Fisher's discriminant analysis for category (−) and category (+) of six endomyocardial biopsy findings obtained from the principal scores (two principal scores in this study).

Although any single histologic finding may not be specific for dilated cardiomyopathy, combined semiquantitative

analysis can show the importance of the histologic features in this disease. We found a close correlation between proliferation of collagen fibers and hypertrophy of myofibers (Table 3). The pathologic process of dilated cardiomyopathy may provoke proliferation of collagen fibers associated with hypertrophy of myofibers. It appears that the myocardium is damaged because of some unknown cause and is replaced by collagen fibers. The residual myocardium may show compensatory hypertrophy. The other findings in our model seem to develop independently.

Simple statistical analysis with Student's *t* test (Fig. 2) suggested a relation between the ratio of end-systolic stress to end-systolic volume index and the degree of hypertrophy of myofibers and between the ejection fraction and proliferation of collagen fibers in dilated cardiomyopathy; the heart with reduced contractility had more hypertrophy of myofibers and proliferation of collagen fibers. To confirm these results, principal component analysis and Fisher's discriminant analysis were employed.

Principal component analysis determined two pairs of important factors in the control of cardiac performance: ejection fraction and end-systolic stress as the first principal component and ratio of end-systolic stress to end-systolic volume index as the second principal component. Fisher's discriminant analysis of these results clearly revealed a close correlation between proliferation of collagen fibers and the first and second principal components that reflect cardiac contractility. The increased proliferation of collagen fibers resulted in a lower ejection fraction and higher end-systolic stress, leading to a decreased ratio of end-systolic stress to end-systolic volume index. Because Spearman rank test suggested a close correlation between proliferation of collagen fibers and hypertrophy of myofibers, we expected the same result in relation to cardiac contractility and two categories, that is, categories (+) and (−) of hypertrophy of myofibers by Fisher's discriminant analysis. However, there was no significant relation between contractility indexes and hypertrophy of myofibers. This result might be due to reduced sensitivity and increased specificity by utilizing any type of multivariate analysis (25).

Current concepts and future aspects. It has been accepted that increased proliferation of collagen fibers occurs with loss of contractile materials after depressed contractility. Kunkel et al. (9) showed that interstitial fibrosis is more prominent in the advanced stage than in the early stage of this disease. Schwarz et al. (8) reported that myocardial fiber diameter and interstitial fibrosis had a significant inverse correlation with the ejection fraction. This result agrees in part with our study. Despite the compensatory hypertrophy of the myofibers in the residual myocardium, the causative mechanism of increased collagen fibers and depressed contractility in dilated cardiomyopathy is unknown. Histochemical and cytochemical analysis of biopsy tissues may provide a clue to the cause of dilated cardiomyopathy.

Limitation of the present study. The specimens obtained by endomyocardial biopsy are small (about 1 to 3 mm^3) and may represent only a small part of the myocardium in a whole ventricle. Because dilated cardiomyopathy is a diffuse myocardial disease (5), more or less the same disease process should be present throughout the ventricles. Although we performed right endomyocardial biopsy in this study, it has been reported (26) that the histologic features in the right and left endomyocardial biopsies from the same patient resemble each other, with involvement of both ventricles in almost all cases of dilated cardiomyopathy. The previous report (4) from our department of 33 patients with idiopathic cardiomyopathy showed a positive correlation of the histologic changes between right and left endomyocardial biopsies from the same patient ($r = 0.41$, $p < 0.05$). Endomyocardial biopsy with Konno's bioptome (27) is a safe way to obtain multiple specimens during cardiac catheterization. The advantage of this method is that it permits simultaneous comparison of hemodynamic data and histologic findings, which is not possible in autopsy studies of the heart.

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Appendix

For the semiquantitative analysis of histologic findings, we designed a scoring system for the features of biopsy specimens (4). The morphologic findings were 1) disarray of myofibers, 2) hypertrophy of myofibers, 3) scarcity of myofibrils, 4) nuclear changes, 5) vacuolization, and 6) proliferation of collagen fibers. We defined five grades for findings 1, 3, 4, 5 and 6: grade (−), no apparent change; (1+), minimal change; (2+), moderate change; (3+), marked change; and (4+), very severe abnormality. The shortest diameter of cardiocytes in nucleated transverse section was measured by an ocular micrometer disc with a line scale in a sample stained with hematoxylin-eosin. Hypertrophy of myofibers (finding 2) was quantified with averaged diameter (of at least 100 cardiocytes): grade (−), less than 16 μm; (1+), 16 to 20 μm; (2+), 20 to 24 μm; (3+), 24 to 28 μm; and (4+), >28 μm.

We categorized two subgroups arbitrarily according to the grade of histologic findings: category (−) and category (+). For scarcity of myofibrils, nuclear changes, vacuolization and proliferation of collagen fibers, category (+) signifies definitely significant histologic findings of grade (2+) or more. Category (−) indicates no significant histologic findings and includes grade (−) and grade (1+). For disarray of myofibers, category (+) indicates grade (3+) or (4+). For hypertrophy of myofibers, category (+) indicates grade (1+) or more.

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