A Histopathological Study of Dilated Cardiomyopathy  
—with Special Reference to Clinical and Pathological Comparisons of the  
Degeneration-predominant Type and Fibrosis-predominant Type  

SACHIO KAWAI, M.D. AND RYOZO OKADA, M.D.  

Dilated cardiomyopathy (DCM) is defined as a myocardial disease of unknown cause with ventricular dilatation. The age at onset, course and prognosis of this disease varies greatly. The view that DCM is not a homogeneous condition, but is a multifactorial disease, is gaining general acceptance. In contrast to hypertrophic cardiomyopathy that shows myocardial disarray as a characteristic lesion, no specific lesion exists in DCM. Myocardial fibrosis degeneration and myocyte hyper trophy are observed as histological findings of DCM. Because of this broad array of histological findings, analysis of DCM on the basis of the morphology is very difficult; thus, there is no widely accepted consensus.

However, it seems unreasonable to categorize dilated hearts with diffuse fibrosis and with scarce fibrosis under a single pathological nomenclature because of ventricular dilatation (Fig. 1). We re-examined the histology of DCM and classified the disease into subgroups showing similar findings. The clinical features and causes of the subgroups and their ranks in the disease will be discussed.

MATERIALS AND METHODS

Of 56 autopsy cases clinically suspected of being DCM collected from various institutes in Japan and the cooperative study of the Research Committed of Idiopathic Cardiomyopathy, 44 cases without ischemic cardiomyopathy, amyloidosis, hemochromatosis or mitral cleft were selected. Of these 44 cases, eight hearts were assigned to the chronic myocarditis group; these consisted of two with clinical findings of myocarditis, followed by a DCM-like condition, and showing definite inflammatory cell infiltration at autopsy and six cases of DCM exhibiting definite diffuse cell infiltration. Controls consisted of 10 cases of malignant tumor without diabetes mellitus, significant coronary stenosis or cardiac disease (Table 1).

METHODS

For histological investigation, sections including the horizontal section of both ventricles were embedded by the routine method, cut at 6 microns, stained with hematoxylin and eosin, azan and Elastica-van Gieson and examined under a light microscope. Using a 25-point eye-piece (Integrating eye-piece I of Zeiss), the compact layer of left ventricle in the azan-stained specimens was completely scanned in a 40-fold field (Olympus BH-2). The number of points on definite collagen fibers were divided by the sum of the number of points on myocardial cells and that of points on collagen fiber to obtain % area of fibrous. The number of myocardial cells comprising the wall was examined by a modification of Suwa's method. Three sampling lines perpendicular to the compact layer were drawn from the outer to inner layers, and the number of myocardial fiber intersecting the lines was determined by using IBAS-1 (Zeiss). The resultant value was divided by three to obtain the
number of myocardial cells comprising the compact layer (Nf). Determinations were carried out at three sites, the anterior and posterior walls of the left ventricle and interventricular septum, and the mean was used. In addition, the diameter of each myocardial cell at the point of intersection with a sampling line was measured with IBAS-1, and the mean of all measurements was used as an estimated diameter.

Myocardial degeneration was divided into three stages from (−), which is similar to the control group, to (+++) representing marked degeneration (Fig. 2).

Clinical parameters consisted of age, sex, total clinical course, duration of decompensation from the onset of nocturnal dyspnea or dyspnea on effort to death from congestive heart failure, cardiothoracic ratio (CTR), electrocardiographic...
TABLE I CLINICAL FEATURES OF THE PATIENTS WITH DILATED CARDIOMYOPATHY, CHRONIC MYOCARDITIS AND CONTROLS

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Pts. (female)</th>
<th>Age (y-o)</th>
<th>Total clinical course (mo.)</th>
<th>Duration of decompensation (mo.)</th>
<th>CTR</th>
<th>Conduction disturbances</th>
<th>CHF</th>
<th>Cause of death</th>
<th>SD</th>
<th>others</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>36 (8)</td>
<td>45.1</td>
<td>NS</td>
<td>94.3</td>
<td>NS</td>
<td>35.7</td>
<td>66%</td>
<td>33%</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>chr. myocarditis</td>
<td>8 (4)</td>
<td>43.8</td>
<td>NS</td>
<td>72.1</td>
<td>NS</td>
<td>19.1</td>
<td>67%</td>
<td>75%</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>10 (1)</td>
<td>63.5</td>
<td>NS</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt; 50%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CTR = cardiothoracic ratio; CHF = congestive heart failure; SD = sudden death; DCM = dilated cardiomyopathy; NS = not significant.

change and cause of death.

CLASSIFICATION

DCM was histologically divided into Types I and II. Type I represented severe diffuse fibrosis (over 25% of the area) in the compact layer of the left ventricle (fibrosis-predominant type9). Type II (non-fibrous type) was subdivided, depending on the severity of myocardial degeneration, into Type IIa (degeneration-predominat type) with extensive marked degeneration (++), Type IIc (nonspecific type) showing no appreciable differences from control group and Type IIb (intermediate type) with less advanced and less extensive degeneration. Chronic myocarditis was classified as Type III (Fig. 3).

Student's unpaired t-test was used for statistical analysis.

RESULT

Table I shows the clinical data for DCM, chronic myocarditis and control groups. No significant differences were seen with respect to the total clinical course or duration of decompensation. The CTR values on chest X-ray film were also similar. Conduction disturbance was more frequent in the chronic myocarditis group.

Table II shows the clinical data for the subsets (Types I and IIa-c and chronic myocarditis. Total clinical course was extended in the order of Types IIa, IIb and IIc with no significant difference, Type IIa showing the shortest course. The 3 subsets showed similar CTR values.

As associated conditions, Table III shows family history, alcohol intake, preceding symptom of common cold, delivery and other associated diseases. Moderate alcoholicism was found in 64% of the Type IIc cases. Postpartum cardiomyopathy belonged to Type IIa, and atrophy of

Fig.2. Myocardial degeneration in dilated cardiomyopathy.
(A): (−), H-E stain, ×400. (B): (+), H-E stain, ×200. (C): (++), H-E stain, ×100.
Fig. 3. Schema of the classification of DCM.

### TABLE II CLINICAL FEATURES OF THE PATIENTS WITH DCM SUBTYPES AND CHRONIC MYOCARDITIS

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Pts (female)</th>
<th>Age</th>
<th>Total clinical course (m.)</th>
<th>Duration of decapsulation (m.)</th>
<th>CTR (%)</th>
<th>Conduction disturbances (%)</th>
<th>Cause of death</th>
<th>Others</th>
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<tbody>
<tr>
<td>I</td>
<td>9 (2)</td>
<td>44.2</td>
<td>71.7</td>
<td>35.4</td>
<td>65</td>
<td>67</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>IIa</td>
<td>4 (2)</td>
<td>29.3</td>
<td>51.0</td>
<td>21.7</td>
<td>67</td>
<td>25</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>12 (3)</td>
<td>42.9</td>
<td>82.4</td>
<td>34.0</td>
<td>65</td>
<td>42</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>c</td>
<td>11 (1)</td>
<td>53.8</td>
<td>141.6</td>
<td>46.7</td>
<td>68</td>
<td>9</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>8 (4)</td>
<td>40.9</td>
<td>78.7</td>
<td>19.3</td>
<td>67</td>
<td>75</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01
Abbreviations: same as those in Table I

### TABLE III ASSOCIATED CONDITIONS IN THE PATIENTS WITH DCM SUBTYPES AND CHRONIC MYOCARDITIS

<table>
<thead>
<tr>
<th>Groups</th>
<th>Family History</th>
<th>Alcohol intake</th>
<th>Preceding symptom of common cold</th>
<th>Delivery</th>
<th>Other disease</th>
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<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIa</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IIb</td>
<td>12</td>
<td>0</td>
<td>2 (17%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IIc</td>
<td>11</td>
<td>0</td>
<td>7 (64%)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

### TABLE IV HISTOPATHOLOGICAL FEATURES

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Pts</th>
<th>pm.</th>
<th>HW (g)</th>
<th>Wall thickness 1/2 (ant + post LV) (mm)</th>
<th>% area of fibrosis</th>
<th>Nf</th>
<th>Cell size (μ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>4°37'</td>
<td>511</td>
<td>8.7</td>
<td>39.6</td>
<td>140</td>
<td>17.9</td>
</tr>
<tr>
<td>IIa</td>
<td>4</td>
<td>2°33'</td>
<td>468</td>
<td>7.6</td>
<td>13.1</td>
<td>140</td>
<td>16.4</td>
</tr>
<tr>
<td>b</td>
<td>12</td>
<td>5°40'</td>
<td>575</td>
<td>7.8</td>
<td>17.3</td>
<td>223</td>
<td>15.1</td>
</tr>
<tr>
<td>c</td>
<td>11</td>
<td>2°48'</td>
<td>545</td>
<td>8.1</td>
<td>13.1</td>
<td>275</td>
<td>14.4</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>2°38'</td>
<td>468</td>
<td>NS</td>
<td>28.0</td>
<td>157</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>2°21'</td>
<td>369</td>
<td>10.0</td>
<td>2.2</td>
<td>320</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01
Abbreviations: pm = postmortem duration; HW = heart weight; LV = left ventricle; Nf = number of the myocardial fibers.

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skeletal muscle was observed in the IIa and IIb subsets.

Table IV shows the results of histological

investigation. The postmortem duration tended to be long in Type I and IIb. Significant increase in heart weight was observed in all types. All groups showed a lower value of wall thickness of the left ventricular compact layer than that of the control group, with no statistically significant difference for Type I or IIc. Nf (the number of myocardial fibers of left ventricle) was smallest in Types I and IIa (140), and within Type II, the IIa subset showed significant decrease, compared with the IIb and IIc subsets. Nf of the IIc subset was 275, which was smaller than that of the control group, but was not statistically significant. All groups showed an increase in the size of myocardial cells, compared with the control group, but within the DCM group, there was a difference between the I and IIc subsets alone.

Figure 4 shows the relationship between Nf and myocyte size. In the Type II DCM subgroup, Nf decreases with the severity of degeneration.

Fig.4. Relationship between the number of myocardial fiber and myocyte size.

Fig.5. Histological findings. (A,B): Myocardial disarray in the patients with the fibrosis type DCM. The Disarray was observed even in the subendocardial region of the ventricle (A), and usually coexisted with myocardial fibrosis (B) (H-E stain, x 40). (C): Foci of vacuolar degeneration seen in the control group (H-E stain, x 400). (D): Marked cell infiltration and interstitial fibrosis in the patient with the chronic myocardial group (H-E stain, x 100).

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In the control group, the cell size corresponding to 320 in Nf was 12.6 microns, and in Type III (chronic myocarditis), Nf was decreased to 157, but the cell size was increased to 18.6 microns.

Mild interstitial small round cell accumulation was found in 5 Type I cases, one Type IIa case, 3 Type IIb cases and 3 Type IIc cases. In addition, 4 Type I cases demonstrated myocardial disarray (Fig. 5a, 5b).

DISCUSSION

Although the histological classifications of cardiomyopathy was proposed by Hudson\textsuperscript{10} and Okada,\textsuperscript{11} the clinical classification by the school of Goodwin\textsuperscript{5} is most extensively used. Compared with hypertrophic cardiomyopathy, DCM shows no specific histological findings\textsuperscript{5,5} Various findings are observed in various degrees, with no finding characterizing all types of DCM. For this reason, the pathological research of this disease has been considered to be futile\textsuperscript{5} We feel that the view that regards DCM as a homogeneous disease entity is incorrect. Dilatation is a mere compensation mechanism of heart failure.\textsuperscript{12} Since DCM has been finally recognized as a nonhomogeneous disease, the significance of the reclassification of this disease on the basis of pathological findings is obvious.

For the purpose of defining the disease of the heart muscle itself, we separated a group with a high incidence of fibrosis that corresponds to small amount of residual myocardial mass and subdivided it according to the severity of myocardial degeneration.

We regarded % areas over 25% as showing fibrosis type. The % area differs depending on whether or not the intesitum of myocardium is added to the denominator of the equation and becomes small in the projection method.\textsuperscript{13} Percent areas over 25% correspond to the (+++) rating in usual semiquantitative analysis.

The fibrosis type showed milder wall thinning than that of the non-fibrosis types, four cases exhibiting a thicker wall than that of the normal controls. The diameter of myocytes was large, and Nf was significantly decreased. Four cases showed cardiac insufficiency as a cause of death, and four had sudden or arrhythmic death. It is felt that the latter four patients may have survived if they had been adequately treated. Compared with the non-fibrosis subgroup in which 17 of the 27 patients died of cardiac insufficiency, the patients with fibrosis were speculated to have a compensating ability for cardiac output. This compensation is effective for survival, up to certain stage even under the poor condition of extensive fibrosis and scanty myocytes. The increase in the myocyte diameter in the fibrosis subgroup is attributed to a type of compensation hypertrophy.

It is difficult to evaluate degeneration accurately, and a number of subtypes are known for this condition. Vacuolative degeneration has been cited to be a cause,\textsuperscript{14} but we found this condition in a number of controls (Fig. 5c). We focused attention on lysis of myofibrils,\textsuperscript{15,16} a myocardial contractile element, and examined degeneration in terms of spares myofibrils and swelling of the cytoplasm (Fig. 2b, 2c).

Patients with degeneration type were young and had the shortest total clinical course and duration of decompensation; 3/4 of them died from cardiac insufficiency. These cases could be grouped with juvenile onset and a very poor prognosis. The mild degree of hypertrophy despite a large decrease of Nf, i.e., depletion of myocardial cells, suggests a low compensating ability.

The nonspecific form of DCM showed mild fibrosis for this disease, which was similar to that in the IIa subset (degeneration type), but was associated with depletion of fewer cells and a less decrease in wall thickness. Clinically, this type accounted for the largest proportion of the DCM cases\textsuperscript{17} and showed a high age composition with the longest clinical course.

Chronic myocarditis was accompanied by small round cell infiltration with a connective tissue increase (Fig. 5d) and exhibited a similar age composition, total clinical course and incidence of conduction disturbance to those of the fibrosis type. The disease also showed massive fibrosis, depletion of myocardial cells in a degree lower than those of Types I and IIa alone and advanced myocyte hypertrophy.

In Fig. 4, the mean Nf of the Type III case is 157, with a cell size of 18.6 microns, indicating compensatory hypertrophy against the decrease of Nf. Type I presented a similar pattern, which was close to that of Type III, despite the variations in cell size. Type II showed a different pattern. Against the decrease of Nf, the cell size increased in the order of IIc, Iib and IIa, but this increase was different from that of Type III. If the line connecting the control group and Type III is regarded as indicating the presence of compensatory hypertrophy in nonvalvular dilated
heart, the IIa subtype indicates poor compensatory hypertrophy.

CONCLUSION
We classified 36 DCM autopsy cases according to the severity of fibrosis (% area over 25%) and degeneration and compared them with the chronic myocarditis group (8 cases) and control (10 cases) to establish categories of fibrosis-dominant, degeneration-dominant and nonspecific types.

The fibrosis type was associated with a high incidence of conduction disturbance and involved, as the major lesion, a decrease in myocytes, a contractile element, detected on the basis of the severity of fibrosis and low Nf value (number of myocardial fibers). This type was morphologically and clinically close to chronic myocarditis and included cases exhibiting myocardial disarray.

The degeneration type which was found in a relatively small number of patients, showed a younger age composition, shorter total clinical course, smaller Nf and milder compensatory hypertrophy than those of the nonspecific type. Therefore, myocytes tended to undergo primary degeneration and depletion.

The nonspecific type, which accounted for the largest proportion of the DCM cases, showed a greater age composition with a better prognosis. It was characterized by fibrosis and degeneration that were both mild. The high rate of alcoholism by history suggests the involvement of secondary myocardial injury in the etiology.

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