COMPARATIVE STUDY OF DILATED CARDIOMYOPATHY AND SPECIFIC HEART MUSCLE DISEASES FROM PATHOPHYSIOLOGICAL ASPECTS

— Echocardiographic Observation —

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To investigate the causative factors of dilated cardiomyopathy (DCM), 29 DCM patients were echocardiographically and histopathologically compared with 17 patients with specific heart muscle diseases mimicking DCM. These consisted of 6 cases of myocarditis and 11 of alcoholic heart muscle disease. Myocarditis patients had less dilation of the left ventricle, more marked segmental wall motion abnormality on admission and more extensive myocardial fibrosis than patients with alcoholic heart muscle disease and DCM. Four myocarditis patients died of congestive heart failure before showing a marked dilatation of the left ventricle. The alcoholic heart muscle disease patients revealed diffuse wall motion abnormality on admission. Out of these 8 patients who had abstained showed amelioration. However, in 3 who had not abstained, both wall motion abnormality and dilatation of the left ventricle markedly progressed and 2 died of congestive heart failure. Although the DCM patients as a group showed deterioration throughout the follow-up period, individual patients revealed a variety of echocardiographic and pathological findings, which led to the regrouping of 29 patients with DCM into 2 subgroups. One group had characteristic features similar to these of patients with myocarditis, and the other had characteristics similar to these of patients with alcoholic heart muscle disease. These findings suggested that different causative factors might coexist in DCM.

DILATED cardiomyopathy (DCM) is defined as myocardial disease of unknown cause characterized by cardiac enlargement and contractile dysfunction.¹⁻⁵ It should be distinguished from specific heart muscle disease such as alcoholic heart muscle disease and chronic myocarditis.⁶ However, cases with alcohol abuse do not always show the clinical features simulating DCM.^{7,8} Patients with chronic myocarditis may often be diagnosed as DCM because of lack of

symptoms on acute phase or lack of inflammatory cells in biopsied specimens.⁹⁻¹³ However, although DCM is a general term for myocardial diseases of unknown cause, chronic myocarditis and alcohol abuse may be regarded as causes or accelerating factors in the progression of DCM. As mentioned above, there is some confusion among clinical researchers covering DCM since the discrimination between DCM and specific heart muscle disease is rather difficult.

This study aimed to investigate the causative factors and pathophysiologic aspects of DCM. Echocardiographic and histopathological observations were made in DCM patients and compared with those in pa-

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TABLE I PATIENT PROFILE OF MYOCARDITIC GROUP

	Age (<i>ys</i>)	Sex	NYHA (^o)	BP (mmHg)	CTR (%)	ECG Sv ₁ +Rv ₅ (mV)	M mode echocardiogram				Course
							LVDd (mm)	LVDs (mm)	%FS (%)	LVWT (mm)	
I.K.	26	F	IV	100/62	58	1.3	63	52	17	16	died
M.S.	47	M	III	110/82	72	1.8	61	56	8	19	died
K.N.	51	F	IV	140/88	54	RBBB	60	52	13	16	died
A.H.	46	F	III	105/70	53	1.8	60	45	25	18	died (S.D.)
K.M.	21	M	III	100/70	59	RBBB	60	45	25	16	died (S.D.)
K.M.	53	M	III	124/84	62	3.8	63	54	14	17	died

M: Male, F: Female

NYHA: Classification of New York Heart Association, BP: Blood Pressure, CTR: Cardio-Thoracic Ratio, RBBB: Right Bundle Branch Block, LVDd(s): Left Ventricular End-diastolic (End-systolic) Dimension, %FS: %Fractional Shortening, LVWT: Left Ventricular Wall Thickness, S.D.: Sudden Death

TABLE II PATIENT PROFILE OF ALCOHOLIC GROUP

	Age (ys)	Sex	History of alcohol abuse	NYHA (^o)	BP (mmHg)	CTR (%)	ECG SV ₁ +RV _s (mV)	M mode echocardiogram				Course
								LVDd (mm)	LVds (mm)	%FS (%)	LVWT (mm)	
K.M.	44	M	125ml × 15 Y	III—II	110/80	58	RBBB	70	59	15	19	died (S.D.)
A.H.	50	M	150ml × >10 Y	III	110/68	65	4.2	76	66	13	18	alive
M.S.	52	M	150ml × 24 Y	IV	145/85	65	4.5 af	70	53	25	24	alive
S.U.	59	M	250ml × 25 Y	III	95/60	59	1.6	62	51	18	19	alive
K.H.	49	M	125ml × 20 Y	III	126/86	55	4.8	83	73	12	18	alive
H.T.	61	M	100ml × 40 Y	IV	132/78	56	5.6	72	60	17	18	alive
I.N.	51	M	125ml × 28 Y	III	124/66	62	2.9 af	64	52	18	18	alive
M.O.	57	M	100ml × 30 Y	III	122/80	55	2.8 af	63	52	17	18	alive
K.K.	42	M	125ml × 20 Y	IV	110/80	66	5.8	67	53	21	20	died
Y.K.	41	M	150ml × 25 Y	III	120/80	57	3.3 af	70	65	7	19	alive
O.I.	54	M	125ml × 20 Y	III	110/70	76	LBBB af	80	72	10	20	died

History of alcohol abuse: daily ethyl alcohol intake (ml) × duration of alcohol abuse (years)

M: Male, NYHA: Classification of New York Heart Association, BP: Blood Pressure, CTR: Cardio-Thoracic Ratio, RBBB: Right Bundle Branch Block, LBBB: Left Bundle Branch Block, af: Atrial Fibrillation, LVDd(s): Left Ventricular End-diastolic (End-systolic) Dimension, %FS: % Fractional Shortening, LVWT: Left Ventricular Wall Thickness, S.D.: Sudden Death

tients with specific heart muscle disease having clinical features simulating DCM.

MATERIALS AND METHODS

Patient selection: Seventeen patients with specific heart muscle disease mimicking DCM and 29 with DCM admitted to the 1st Department of Internal medicine of Kobe University Hospital from 1977 to 1986, were subjected and followed up for more than 12 months (mean 28—6 months) by echocardiography. The features mimicking DCM

were defined by echocardiographic findings with both left ventricular end-diastolic dimension (LVDd) larger than 60 mm and fractional shortening (%FS) less than 25%. The 17 patients with features mimicking DCM were sub-divided into 2 groups according to the following clinical diagnoses: 6 with myocarditis (myocarditic group), and 11 with alcoholic heart muscle disease (alcoholic group). Myocarditis was diagnosed by a flu-like episode followed by electrocardiographic changes, elevation of myocardial enzyme and/or accumulation of pericardial

TABLE III PATIENT PROFILE OF DCM GROUP

	Age (ys)	Sex	NYHA (°)	BP (mmHg)	CTR (%)	ECG SV ₁ +RV ₅ (mV)	M mode echocardiogram				Course
							LVDd (mm)	LVDs (mm)	%FS (%)	LVWT (mm)	
A.I.	48	M	III	130/70	71	4.6 af	64	48	25	22	alive
A.O.	50	M	II-III	134/80	57	4.1 af	63	51	24	21	alive
H.U.	45	M	III	116/72	62	5.0	79	70	11	19	died
M.U.	13	F	III	110/80	61	2.0	67	59	12	17	died
S.K.	68	M	III	102/80	54	3.7	66	54	18	18	alive
Y.K.	61	F	II-III	100/68	66	7.2	78	70	10	18	died
Y.K.	50	F	III	122/70	56	5.4	63	53	16	18	alive
H.S.	29	F	II	110/78	46	1.8 af	60	49	18	19	alive
T.S.	42	M	IV	90/70	65	LBBB	64	57	11	19	died
S.S.	50	M	III	118/68	59	3.0 af	61	46	25	19	alive
J.S.	54	M	II-III	136/80	66	5.4	63	56	11	20	alive
F.H.	59	M	III	100/80	61	1.4 af	75	62	22	18	died (S.D.)
M.M.	25	M	III	103/80	65	0.9	71	65	8	20	died
T.M.	50	M	III	124/74	53	4.0	65	53	18	20	alive
T.Y.	46	M	III	118/78	57	3.1	68	52	24	20	died (S.D.)
K.H.	46	M	III	120/68	64	3.5 af	72	58	19	22	alive
K.I.	26	F	IV	102/70	62	1.3	61	50	18	16	died
N.K.	51	F	II	140/82	54	1.8	60	52	13	18	died (S.D.)
K.M.	44	M	IV	106/80	64	RBBB	68	58	15	19	died (S.D.)
K.S.	52	F	III	110/78	54	4.9	67	58	13	18	alive
S.N.	50	M	IV	108/68	71	LBBB	75	68	9	18	alive
S.H.	52	F	III	110/72	67	4.5	67	58	13	18	alive
T.W.	50	M	IV	108/70	61	LBBB	79	70	12	19	alive
K.I.	16	M	II	112/70	55	5.5	65	50	23	18	alive
S.K.	32	M	III	114/64	52	3.5	63	52	18	18	alive
Y.K.	37	F	III	82/54	56	1.2	67	59	12	18	died (S.D.)
K.A.	62	F	III	126/64	74	2.3	63	53	15	20	alive
Y.A.	53	M	III	106/70	52	2.8 af	60	52	13	19	alive
H.A.	46	F	III	94/54	59	3.2	64	53	18	19	died

M: Male, F: Female

NYHA: Classification of New York Heart Association, BP: Blood Pressure, CTR: Cardio-Thoracic Ratio. LBBB: Left Bundle Branch Block, RBBB: Right Bundle Branch Block, af: atrial fibrillation, LVDd(s): Left Ventricular End-diastolic (End-systolic) Dimension, %FS: %Fractional Shortening, LVWT: Left Ventricular Wall Thickness, S.D.: Sudden Death

effusion, or by the presence of inflammatory cells in endomyocardial biopsy.¹⁴ According to the diagnostic criteria, two cases of myocarditis were shown to suffer from acute myocarditis, showing progressive cardiac dilatation, the remaining 4 patients were diagnosed as having myocarditis by endomyocardial biopsy (Table I). All patients in the alcoholic group had a history of alcohol abuse of more than 100 ml of ethylalco-

hol daily for more than 10 years (Table II). DCM was diagnosed according to WHO/ISFC task force.⁶ Therefore, patients with cardiac diseases with known causes and those resulting from systemic diseases were carefully excluded from DCM group (Table III).

Of these 46 patients, 39 underwent left ventriculography and coronary angiography, all of whom showed marked left ventricular

Fig. 1. Segmentation of the left ventricular wall by 2 dimensional echocardiography. Left: parasternal short axis view at mitral level, Center: parasternal short axis view at papillary muscle level, Right: apical long axis view. IVS: Interventricular Septum, MV: Mitral Valve, PMP: Posteromedial Papillary Muscle, ALP: Anterolateral Papillary Muscle, Segment 1 and 5: anterior wall of the left ventricle, Segment 2 and 6: lateral wall of the left ventricle, Segment 3 and 7: posterior wall of the left ventricle, Segment 4a and 8a: anterior portion of interventricular septum, Segment 4p and 8p: posterior portion of interventricular septum, Segment 9: apex

Fig. 2. Echocardiographic parameters at the initial study in each group. MC: Myocarditic Group, AL: Alcoholic Group, DCM: Dilated Cardiomyopathy Group, Left upper: Left ventricular diastolic dimension, Middle upper: % Fractional shortening, Right upper: Left ventricular wall thickness, Left bottom: Wall motion abnormality index, Right bottom: Non-uniformity index

Fig. 3. Changes in echocardiographic parameters between the initial and the last study in each group.

MC: Myocarditic Group, AL: Alcoholic Group, DCM: Dilated Cardiomyopathy Group, Left upper: Left ventricular diastolic dimension, Middle upper: % Fractional shortening, Right upper: Left ventricular wall thickness, Left bottom: Wall motion abnormality index, Right bottom: Non-uniformity index

dilatation and diminished left ventricular contractility, however, no patient had significant coronary stenosis. Coronary artery disease was considered unlikely in the remaining patients, because they had no typical episode of angina pectoris and had no coronary risk factors. Right ventricular endomyocardial biopsy was performed in 37 patients.

During the follow-up period, 21 patients died and 15 of them underwent autopsy which revealed that their coronary arteries were intact.

Echocardiography: Echocardiographic studies were performed using Toshiba SSH-11A or SSH-40A. M mode echocardiogram was recorded on strip chart by a line scan recorder. Left ventricular end-diastolic and end-systolic dimension (LVDd and LVDs) as well as the sum of interventricular and posterior wall thicknesses (IVWT) were mea-

sured. The percent fractional shortening (%FS) was calculated. Two dimensional echocardiograms using the parasternal and apical approach were recorded on video tape. To evaluate the segmental wall motion of the left ventricle, the left ventricular wall was divided into 11 segments consisting of anterior (segment 1 and 5) lateral (segment 2 and 6), posterior (segment 3 and 7), antero-septal (segments 4a and 8a) and postero-septal walls (segments 4p and 8p) at mitral and papillary muscle levels and apex (segment 9) as shown in the schematic diagram of Fig. 1.

The wall motion in each segment was evaluated and ranked with 4 grade scales by visual inspection based on both wall excursion and wall thickening (normal=0, hypokinesis=1, severe hypokinesis=2, akinesis or dyskinesis=3). In each patient

Fig. 4. Changes in the correlation between left ventricular diastolic dimension and wall motion abnormality index in myocarditic and alcoholic groups. The correlation between left ventricular diastolic dimension and wall motion abnormality index in the alcoholic group was located on the right of that in the myocarditic group. ●: myocarditic group, ○: alcoholic group (abstinence), ⊙: alcoholic group (non-abstinence), +: died of heart failure, →: initial study to last study

the average value and standard deviation of the scales for the 11 segments were calculated. The former was used as the index of severity and extension of wall motion abnormality (wall motion abnormality index) and the latter was used as the index of non-uniformity of wall motion abnormality (non-uniformity index)¹⁵ (Fig. 1)

M mode echocardiographic measurements were separately made by 2 specialist echocardiographers, and the average values used. The evaluation of segmental wall motion abnormalities with 2 dimensional echocardiography was also made separately by 2 specialists; when different evaluations were made, a third expert was called up for the assessment.

Endomyocardial biopsy: Right ventricular endomyocardial biopsy was performed in 37 patients comprising 5 in the myocarditic group, 9 in the alcoholic group and 23 in DCM. For the biopsied specimens with Azan stain, the rate of myocardial fibrosis (% Fibrosis) was calculated by the point counting method (counting 200 points)¹⁶ and the mean diameter of 30 myocardial cells was measured for Hematoxylin-Eosin stain specimens.

RESULTS

1) Initial echocardiographic examination (Fig. 2):

The LVDd in the myocarditic group was significantly smaller than that in the alcoholic group (60.8 ± 5.0 mm vs 70.6 ± 6.8 mm; $p < 0.02$). The LVDd in the DCM group ranged between those in the myocarditic and alcoholic groups, but revealed no significant difference from them. Percent FS showed no significant difference among the 3 groups. Left ventricular wall thickness was significantly smaller in the myocarditic group than in the alcoholic and DCM groups (17.0 ± 1.2 mm vs 19.0 ± 2.0 mm; $p < 0.05$, 17.1 ± 1.2 mm vs 19.1 ± 1.5 mm; $p < 0.01$ respectively). Wall motion abnormality index also revealed no significant difference among the 3 groups. However, non-uniformity index was significantly larger in the myocarditic group than in the other 2 groups (1.1 ± 0.2 vs 0.5 ± 0.1 ; 1.1 ± 0.2 vs 0.6 ± 0.3 ; $p < 0.005$ respectively). It was widely distributed in the DCM group, while narrowly in the myocarditic and alcoholic groups, respectively, which were clearly separated from each other by the average of 0.8 through these 2 groups.

Fig. 5. Changes in the correlation between left ventricular diastolic dimension and wall motion abnormality index in dilated cardiomyopathy group. The correlation between left ventricular diastolic dimension and wall motion abnormality index in diffuse wall motion abnormality group ($\text{NUI} < 0.8$) was located on the right of that in the segmental wall motion abnormality group ($\text{NUI} \geq 0.8$).

●: non-uniformity index ≥ 0.8 , ○: non-uniformity index < 0.8 , +: died of heart failure, →: initial study to last study

2) Follow-up study by echocardiography (Fig. 3):

In the myocarditic group, LVDd and wall motion abnormality index increased (60.8 ± 5.0 mm to 68.0 ± 6.2 mm; $p < 0.05$, 1.4 ± 0.4 to 1.8 ± 0.41 ; $p < 0.05$ respectively) while %FS and LVWT decreased ($17.0 \pm 6.8\%$ to $12.0 \pm 4.0\%$; $p < 0.05$, 17.0 ± 6.8 mm to 14.8 ± 1.4 mm; $p < 0.05$ respectively). Of the 6 patients, 4 died of congestive heart failure during the follow-up period.

In the alcoholic group, 8 patients who continued abstinence revealed different clinical courses from 3 patients who continued heavy drinking. In the former, LVDd decreased (70.7 ± 7.1 mm to 64.1 ± 6.9 mm; $p < 0.01$) and %FS and wall motion abnormality index were improved ($16.9 \pm 3.9\%$ to $21.7 \pm 4.5\%$; $p < 0.005$, 1.1 ± 0.6 to 0.8 ± 0.6 ; $p < 0.005$ respectively). In the latter, however, LVDd increased (mean 72.3 mm to 81.0 mm) and %FS and wall motion abnormality index deteriorated (mean 12.7% to 7.7%, mean 1.4 to 2.0 respectively).

Throughout the follow-up period, non-uniformity index was larger in the myocarditic group than in the alcoholic group (1.0 ± 0.1

Fig. 6. Percent fibrosis and myocardial cell diameter in the biopsied myocardial specimen in myocarditic, alcoholic and dilated cardiomyopathy groups

MC: Myocarditic Group, AL: Alcoholic Group, DCM: Dilated Cardiomyopathy Group

vs 0.4 ± 0.1 ; $p < 0.001$ at last study). In the DCM group, LVDd increased (67.2 ± 6.2 mm to 69.2 ± 8.0 mm; $p < 0.05$) and %FS

Fig. 7. Percent fibrosis and myocardial cell diameter in the biopsied myocardial specimens in dilated cardiomyopathy
NUI: non-uniformity index

and wall motion abnormality index deteriorated ($15.9 \pm 5.1\%$ to $14.0 \pm 5.5\%$; $p < 0.05$, 1.2 ± 0.6 to 1.5 ± 0.7 ; $p < 0.01$ respectively). LVWT decreased (19.1 ± 1.5 mm to 17.9 ± 2.9 mm; $p < 0.05$), and non-uniformity index showed no significant change. However, individual patients in the DCM group disclosed different alterations of the echocardiographic parameters. Percent FS and wall motion abnormality index were improved in 5 and 7 patients, respectively, and the LVWT increased in 5.

3) Characteristics of the alterations of echocardiographic parameters and the findings of endomyocardial biopsy:

Four patients in the myocarditic groups showed severe wall motion abnormality and died of congestive heart failure before the LVDd reached 75 mm. The left ventricle was more severely dilated in the alcoholic group than in the myocarditic groups, although their wall motion abnormality indices showed no significant difference. Especially, 2 patients in the alcoholic group died of congestive heart failure after marked progression of left ventricular dilatation (LVDd: 83 mm, 87 mm respectively). The correlation between left ventricular end-diastolic dimension and wall motion abnormality index in the alcoholic group was located on the right of that in the myocarditic group (Fig. 4).

Although wall motion abnormality index generally increased along with left ventricular dilatation in the DCM group, the patients disclosed different alterations of the echocardiographic parameters individually. According to the values of non-uniformity index, patients in this group were subdivided into 2 subgroups [segmental wall motion abnormality group: non-uniformity index ≥ 0.8 and diffuse wall motion abnormality group: non-uniformity index < 0.8 (0.8 is the average of non-uniformity index through in the myocarditic and alcoholic groups)]. The former resembled the myocarditic group and the latter the alcoholic group in the relationship between left ventricular end-diastolic dimension and wall motion abnormality index (Fig. 5).

The findings of biopsied myocardium showed no significant difference in myocardial cell diameters among 3 groups. However, in the 4 patients in the myocarditic group, inflammatory cell infiltration was observed and %Fibrosis in this group was greater than in the alcoholic and DCM groups ($26.5 \pm 4.2\%$ vs $12.3 \pm 4.2\%$; $p < 0.001$, $26.5 \pm 4.2\%$ vs $13.3 \pm 7.5\%$; $p < 0.005$ respectively) (Fig. 6). Moreover, the findings of biopsied myocardium were also different between the 2 subgroups in DCM. Percent fibrosis was significantly larger in the segmental wall motion abnormality group than in the diffuse wall motion abnormality

group ($19.3 \pm 11.6\%$ vs $10.8 \pm 4.0\%$; $p < 0.05$), while myocardial cell diameter showed no significant difference between 2 groups (Fig. 7).

DISCUSSION

Dilated cardiomyopathy, which is defined as a myocardial disease of unknown cause, is considered to reveal dilatation of the left ventricle as a result of diffusely affected myocardium. Recently it has been reported that wall motion abnormalities in DCM are not always diffuse but frequently segmental by left ventriculography¹⁷⁻²⁰ and radionuclide ventriculography;²¹ however, it is not clear why the wall motion abnormality progresses segmentally in DCM. Some mechanisms are believed to be the causes of segmental wall motion abnormality such as progress in segmental myocardial ischemia due to transient occlusion of coronary arteries or small vessel abnormality, ventricular conduction disorders, loading conditions to right and left ventricles or regional abnormalities of myocardial metabolism.¹⁷⁻²² In the present study we confirmed that the subjects had neither episode nor lesions of coronary artery disease, although some patients with myocardial infarction without coronary artery lesions may not be completely excluded. It is known that the wall motion of the left ventricle is much influenced by the loading conditions or conduction disorders. Therefore, to evaluate left ventricular wall motion abnormality exactly, we referred to wall thickening at the site of observation.¹⁵ Geltman et al indicated that regional abnormality of myocardial metabolism was observed in DCM;²³ which might suggest that segmental wall motion abnormality reflects the pathogenesis of DCM.

Dilated cardiomyopathy is probably caused by several factors such as toxic, metabolic and inflammatory factors.^{1,2,5} In particular relation between DCM and viral myocarditis has been noted.^{9-13,24-26} The experimental study reported that mice with viral myocarditis showed DCM-like features as a result of progress in the myocardial fibrosis.²⁷ Viral myocarditis is now being regarded as one of the causes of DCM. Although alcoholic heart muscle disease sometimes mimics DCM, its pathogenesis is

not elucidated in detail.²⁸⁻³⁰ However, it has been reported that histochemical and electron microscopic study showed myocardial cell degeneration in alcoholics and alcohol fed mice;³¹⁻³⁴ and a heart muscle disorder appeared in alcohol fed rats which were also given catalase inhibitor.³⁵ Thus, massive consumption of ethylalcohol may result in metabolic myocardial damage which leads to severe contractile failure of the left ventricle.

In this study, the progression of left ventricular wall motion abnormality was clearly different between the patients with myocarditis and those with alcoholic heart muscle disease. The former showed severe wall motion abnormality which progressed segmentally even when left ventricular dilatation was not so severe, and died of congestive heart failure before the left ventricle revealed prominent dilatation. Several reports have indicated that some patients with myocarditis showed segmental wall motion abnormality which resembled that in myocardial infarction.^{36,37} Therefore, the myocardial disorder may progress non-uniformly and segmental wall motion abnormality is thought to be one of the characteristic features in myocarditis. Another characteristic feature in this disease may be relatively restrictive left ventricle which is probably caused by greater myocardial fibrosis. This restriction results in easier reduction of contractility because of lack of sufficient effect of the Starling's law. On the other hand, the alcoholic group had diffuse wall motion abnormality and showed marked dilatation of the left ventricle in deteriorating patients with continuing alcohol abuse. These features were consistent with the biopsy findings of low myocardial fibrosis rate in this group.

Therefore, it is suggested that in alcoholic heart muscle disease, abstinence relieves the metabolic abnormality of the myocardium due to ethylalcohol and ameliorates the depressed contractility of the myocardium.

The clinical course of DCM was categorized into 2 sub-groups characterized by a similarity to the myocarditic group and the alcoholic group. The wall motion abnormality progressed segmentally in the former group and diffusely in the latter group. Moreover, the grade of %Fibrosis was significantly different between these 2 groups.

These results suggested that patients of DCM consisted of sub-groups with different clinical courses and that echocardiographic evaluation of the left ventricular wall motion abnormality was important for investigating the pathogenesis and prognosis of DCM.

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