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Comparison of Percentage Area of Myocardial Fibrosis and Disarray in Patients With Classical Form and Dilated Phase of Hypertrophic Cardiomyopathy

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Abstract

This study compared the percentage area of myocardial fibrosis and disarray between hypertrophic cardiomyopathy (HCM) and DHCM (progression to dilatation of the left ventricle in patients with HCM, *i.e.*, dilated phase HCM), and investigated whether DHCM is included in the natural course of HCM.

Twenty-six autopsied hearts were studied, 14 from patients with HCM, and 12 from patients with DHCM, classified by age/decade group. The section at the level of the binding site of papillary muscle was used for the morphometrical examination.

In the overall evaluation of both ventricles, all 4 HCM age groups showed percentage area of myocardial fibrosis <10%, and the value gradually increased with age. In contrast, the percentage area of the DHCM cases was over 20%, and these cases showed diffuse massive fibrosis that did not increase with age. The percentage area of myocardial disarray was over 90% in 3 cases with DHCM.

The percentage areas of myocardial fibrosis and disarray of the DHCM hearts were extremely high compared with the HCM hearts, indicating that DHCM is not included in natural course of HCM. Other abnormalities including contractile proteins may be important role in the widespread myocardial disarray leading to massive fibrosis in the pathogenesis of DHCM.

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Key Words

■ **Cardiomyopathies (hypertrophic)** ■ **Cardiomyopathies, other (dilated phase of hypertrophic cardiomyopathy)** ■ **Myocardial fibrosis** ■ **Myocardial disarray** ■ **Natural course**

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by asymmetrical hypertrophy but not dilatation of the left ventricle[1–3]. Many patients with HCM have a relatively good prognosis[4], but recently it has been recognized that patients with HCM occasionally show progression to dilatation of the left ventricle and die of congestive heart failure[5]. This progression of HCM to dilated phase HCM (DHCM) is reported to occur in about 10% of patients with HCM. The important morphologic features of DHCM are massive fibrosis and widespread disarray of the myocardium, which might be responsible for dilatation of the left and right ventricles[6,7]. The course and prognosis of patients with DHCM has not been reported in detail. This study compared the percentage area of myocardial fibrosis and disarray between DHCM and HCM heart and investigated whether DHCM is included in the

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natural course of HCM.

METHODS

Patient population (Table 1)

Twenty-six autopsied hearts were studied, 14 from patients with HCM and 12 from patients with DHCM. Both were categorized with 4 age groups; 10–29, 30–49, 50–69, and 70–80 years old. All 26 patients had been evaluated over the clinical course and were initially diagnosed both clinically and pathologically as having HCM. Each patient met the following criteria: clinical echocardiographic or necropsy demonstration of myocardial disarray, and markedly asymmetric hypertrophied left ventricle at the time of diagnosis of HCM. None of these patients had significant hypertensive, valvular, congenital, or infectious disease that could have caused left ventricular hypertrophy.

Cardiac preparation

After excision of the heart with removal of the great vessels, the bilateral atria were dissected along the atrioventricular groove. The epicardial fat was carefully removed, and then the weight of heart was measured. Before sectioning, the major longitudinal axis of the left ventricle was determined.

Preparation of myocardial specimens

The heart was fixed in 10% formalin under systemic pressure. The 2 ventricles of each heart were sliced at about 1 cm intervals, perpendicular to the major axis of the heart from the apex to the base. These sections were then examined grossly for the assessment of large areas of myocardial fibrosis. The section at the level of the binding site of papillary muscle was used for the morphometrical examination. After estimation of the transverse chamber diameter and wall thickness, the slices were directly embedded in paraffin.

Evaluation of myocardial fibrosis (Fig. 1)

Quantitative analysis was restricted to one slide of both ventricles of the hearts. These samples were stained with hematoxylin-eosin and Masson-trichrome stains. Subsequently, these stained slides were examined with a light microscope equipped with a camera for 35 mm color film slides. Histological slides were made of the anterior, lateral, posterior and septal portions of the left ventricle and the whole portion of the right ventricle. These slides were scanned by a Nikon film scanner (Nikon, Tokyo, Japan) and histological figure files were made in the Tagged-Image File Format (TIFF) with high resolution [2,500 dots per inch (DPI)]. The size and contrast of the histological figures were processed into files for NIH Image using Photoshop version 2.5 (Adobe Systems, USA).

Selected abbreviations and acronyms

DHCM = dilated phase of hypertrophic cardiomyopathy
HCM = hypertrophic cardiomyopathy

In this study, myocardial fibrosis was observed to be organized from massive and fine interstitial fibrosis. For the evaluation of the percentage area of myocardial fibrosis, all figure slides obtained from each portion of transverse myocardial slice were evaluated with a × 10 objective lens and a corresponding computer monitor image. The area of myocardial fibrosis and the area of normal myocardial lesions were determined from estimation of scanned histological figures using NIH Image (1.44).

Evaluation of myocardial disarray (Fig. 2)

The same slides were used for evaluation of the percentage area of myocardial disarray with a × 20 objective lens. Myocardial disarray was evaluated according to the histological criteria of Davies *et al.*[2] and Roberts and Ferrans[8], and was circumscribed with an objective marker on the hematoxylin-eosin histologic slides. The area of myocardial disarray was determined, and the border was circled by the marker directly on the slide. Subsequently, slides with borders were made into 35 mm color histological slides and scanned. The areas of myocardium containing disarray and normal tissue were determined and measured using NIH Image (1.44).

Morphometric calculations: Percentage areas of myocardial fibrosis and myocardial disarray

The percentage of myocardial fibrosis in the ventricular wall of each transverse slide was obtained by dividing the total area of myocardial fibrosis by the total tissue area. To determine the distribution of myocardial fibrosis, the regional percentage areas of myocardial fibrosis in the anterior, lateral, posterior and septal wall of the left ventricle and the whole wall of the right ventricle were calculated. NIH Image was used to measure the area of

Table 1 Patient characteristics

Age group (yr)	Cases	Age (yr)/gender	Cardiac weight (g)
HCM			
10−29	H1-1	12/F	280
	H1-2	27/M	600
30−49	H2-1	31/M	450
	H2-2	48/F	620
50−69	H3-1	53/M	340
	H3-2	56/M	500
	H3-3	58/M	600
	H3-4	61/M	480
	H3-5	61/F	550
	H3-6	64/M	720
70−80	H4-1	71/M	420
	H4-2	74/M	550
	H4-3	78/M	410
	H4-4	81/F	460
DHCM			
10−29	D1-1	15/F	630
	D1-2	16/M	680
30−49	D2-1	42/M	630
	D2-2	46/M	710
50−69	D3-1	50/F	630
	D3-2	56/F	500
	D3-3	59/M	540
	D3-4	61/M	665
	D3-5	61/F	400
	D3-6	64/M	470
	D3-7	65/M	700
	D3-8	67/M	650

Fourteen hypertrophic cardiomyopathy (HCM) patients and 12 dilated phase of hypertrophic cardiomyopathy (DHCM) patients in the age ranges of 10−29, 30−49, 50−69, and 70−80 years old.

each histological preparation in the scanned figure files (TIFF format). The percentage area of myocardial disarray was determined by the same method, by dividing the total area of myocardial disarray by the total tissue area without myocardial fibrosis.

Statistical analysis

Myocardial fibrosis and myocardial disarray were traced and quantified independently by 2 morphologists. Measurements varied by $< 7\%$. Results are presented as mean value $\pm$ SD. Statistical significance for differences between 2 measurements

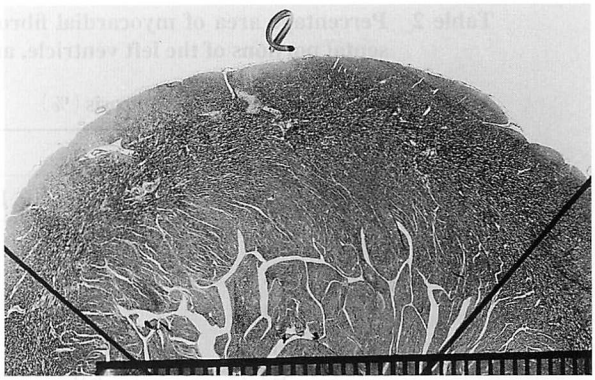

Fig. 1 Histological slide obtained from lateral portion of the left ventricle
Masson-trichrome stain (× 2). Computer monitor (× 10). These corresponding slides were evaluated. The ruler and borderline between each portion are indicated on this figure.

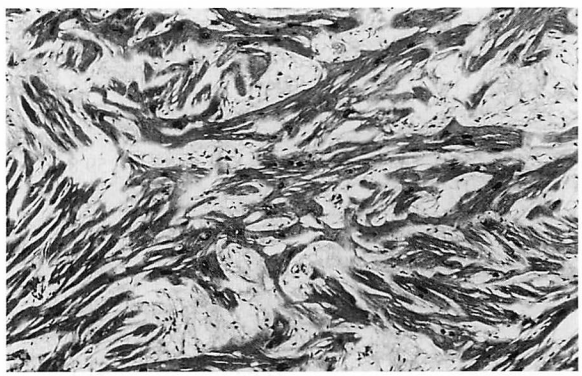

Fig. 2 Myocardial disarray was diffusely present in the posterior wall of HCM case (× 10)

of total area was determined using the unpaired 2-tailed Student's *t*-test. Values of $p < 0.05$ were considered significant.

RESULT

Macroscopic findings

The cardiac weight of each heart is shown in **Table 1**.

Quantitative analysis of myocardial fibrosis (Table 2−B, Fig. 3)

Segmental fibrosis, replacement fibrosis, and interstitial fibrosis were used for the quantitative definition of myocardial fibrosis. NIH Image analysis detected fine interstitial fibrosis which could be traced even if it formed only a single line.

In the total evaluation of both ventricles, each

Table 2 Percentage area of myocardial fibrosis calculated for the anterior, lateral, posterior, and septal portions of the left ventricle, and for the whole left and right ventricles

A. Percentage area of myocardial fibrosis (%)

Age group (yr)	Cases	Site						
		Anterior	Lateral	Posterior	Septal	LV	RV	Total
HCM								
10–29	H1-1	0.4	0.2	0.4	5.2	1.8	0.7	1.6
	H1-2	2.0	1.2	1.6	6.1	2.0	1.3	1.9
30–49	H2-1	5.1	7.3	1.7	3.4	4.1	2.6	3.9
	H2-2	6.9	2.5	2.3	10.7	5.0	5.7	5.1
50–69	H3-1	10.2	9.0	12.4	9.8	10.3	10.7	10.4
	H3-2	1.2	0.9	2.8	2.4	1.7	5.6	2.0
	H3-3	14.6	2.1	4.6	8.8	6.9	2.5	6.0
	H3-4	2.2	3.0	2.2	2.4	2.5	1.1	2.4
	H3-5	15.2	6.8	5.0	3.2	6.8	6.2	6.7
	H3-6	7.4	4.0	12.1	8.6	7.9	6.3	7.7
70–80	H4-1	12.0	6.3	11.7	16.4	11.7	7.1	10.7
	H4-2	6.1	9.5	3.4	3.4	6.1	3.5	5.8
	H4-3	9.6	6.3	5.8	14.0	9.0	13.6	9.6
	H4-4	7.8	7.4	7.6	6.8	7.4	6.5	7.3
DHCM								
10–29	D1-1	59.8	37.6	24.0	19.5	38.0	1.2	34.3
	D1-2	44.7	27.6	31.7	42.8	36.8	39.9	37.3
30–49	D2-1	21.1	11.4	21.1	26.9	18.4	17.2	18.3
	D2-2	27.9	58.1	52.2	17.9	33.3	2.4	28.0
50–69	D3-1	7.4	31.9	29.9	51.9	30.2	9.3	26.3
	D3-2	43.4	18.0	28.0	54.3	34.6	24.7	33.4
	D3-3	41.1	15.6	23.2	39.0	26.7	1.3	22.0
	D3-4	16.5	15.4	25.3	35.2	19.9	27.3	20.5
	D3-5	92.4	25.9	54.3	27.1	44.9	14.2	37.6
	D3-6	41.2	24.5	50.2	37.7	36.6	15.6	33.8
	D3-7	30.2	32.0	35.8	18.7	29.7	19.6	28.6
	D3-8	6.4	25.4	12.6	8.8	12.5	22.6	14.1

B. Percentage area of myocardial fibrosis (%): Total area

	HCM				DHCM		
	H1	H2	H3	H4	D1	D2	D3
Age group (yr)	10–29	30–49	50–69	70–80	10–29	30–49	50–69
Number of patients	2	2	6	4	2	2	8
Mean±SD	1.8±0.2	4.5±0.8	5.9±3.2	8.4±2.2	35.8±2.1	23.2±6.9	27.0±7.9

LV=whole left ventricle; RV=whole right ventricle. Other abbreviations as in Table 1.

age decade of the 14 HCM cases showed < 10% area of myocardial fibrosis, and the value gradually increased with age. In contrast, the percentage area of the 12 DHCM cases was over 20%. The myocardial fibrosis of the DHCM cases was also diffuse, not correlated with coronary arteries, and did not increase with age (**Fig. 3**).

Quantitative analysis of myocardial disarray

Overall evaluation of both ventricles in both

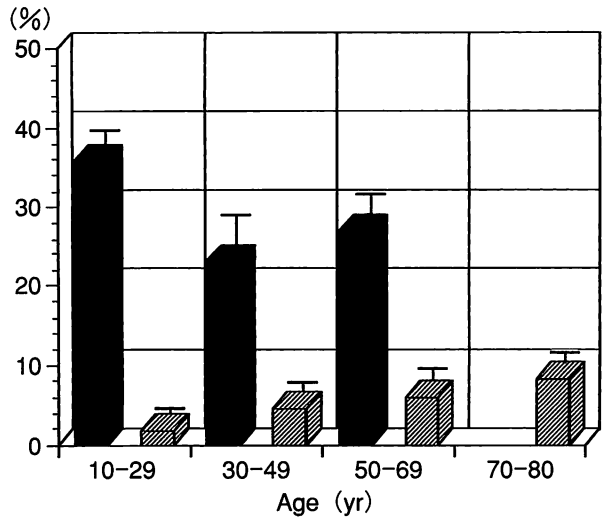

Fig. 3 Graph showing each age group of the HCM cases had < 10% area of myocardial fibrosis and a gradual increase with age, whereas the DHCM cases had over 20% area
Solid bar: DHCM group. Striped bar: HCM group. Each age group; DHCM 10–29: $n=2$, 30–49: $n=2$, 50–69: $n=8$; HCM 10–29: $n=2$, 30–49: $n=2$, 50–69: $n=6$, 70–80: $n=4$.

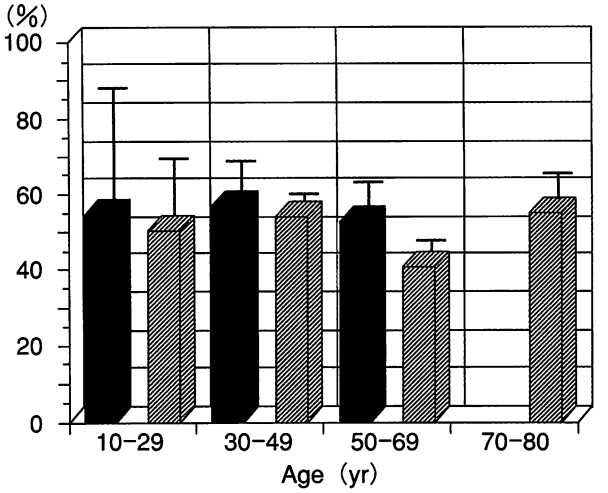

Fig. 4 Graph showing no significant difference in percentage area of myocardial disarray between the HCM and DHCM groups and no increase with age
Solid bar: DHCM group. Striped bar: HCM group. Each age group; DHCM 10–29: $n=2$, 30–49: $n=2$, 50–69: $n=8$; HCM 10–29: $n=2$, 30–49: $n=2$, 50–69: $n=6$, 70–80: $n=4$.

HCM and DHCM hearts found no difference between percentage area of myocardial disarray, and no increase with age (**Fig. 4**). However, by estimating the myocardial disarray of each portion separately, 3 of the DHCM hearts (D1-1, D3-4, D3-5) were revealed to have over 90% myocardial disarray in more than 2 portions of the left ventricular wall. This high percentage area of myocardial disarray is important in morphometrical analysis. Subsequently, in 19 of the 26 total cases, the percentage area of myocardial disarray of the left ventricle was higher than that of the right ventricle, but not significantly so (**Table 3**).

DISCUSSION

Comparison of hypertrophic cardiomyopathy and dilated phase of hypertrophic cardiomyopathy

Compared with the universally verified cases of HCM, there are several unique aspects of DHCM as follows[6]: 1) Dilatation of the left ventricle is marked and mural thrombi are commonly seen at the apex of the left ventricle. 2) The area of fibrosis is extraordinally marked and its distribution is irregular, since fibrosis in HCM is not usually so extensive as in DHCM. 3) The pattern of fibrosis is zonal and massive, and clearly different from the plexiform fibrosis reported by Anderson *et al.*[9] 4) Myocardial disarray is not only observed throughout the left and right ventricles, but is also present closely adjacent to fibrosis. These particular findings in DHCM cases suggest that myocardial disarray might be related to the pathogenesis of fibrosis, although Yutani *et al.*[6] could not clarify how disarray might be related to the pathoetiology of myocardial fibrosis. 5) Clinically, the age of DHCM patients is relatively young and some have a family history of HCM. These findings were confirmed by our present study.

Aside from such differences between HCM and DHCM, this study compared the percentage area of myocardial fibrosis and disarray between HCM and DHCM cases, and clarified whether DHCM is a part of the natural course of HCM. Twenty-six autopsied hearts were studied, 14 from patients with HCM, and 12 from patients with DHCM at 10–29, 30–49, 50–69, and 70–80 years of age. According to Nagata *et al.*[7], there are clinically 2 peaks in the age distribution of DHCM patients, at 10–20 and 50–60 years of age. It is well known that the percentage area of myocardial fibrosis in HCM cases, even those in aged patients, is no more than 10%[4,10]. If DHCM is included in the natural course of HCM, the percentage area of myocardial

Table 3 Percentage area of myocardial disarray calculated for the anterior, lateral, posterior, and septal portions of the left ventricle, and for the whole left and right ventricles

A. Percentage area of myocardial disarray (%)

Age group (yr)	Cases	Site						
		Anterior	Lateral	Posterior	Septal	LV	RV	Total
HCM								
10–29	H1-1	38.4	34.5	47.9	46.9	42.1	4.3	34.7
	H1-2	79.0	63.0	61.2	69.8	68.4	55.3	65.7
30–49	H2-1	53.2	39.3	67.5	61.7	57.2	24.3	52.7
	H2-2	58.4	42.6	61.5	89.3	59.8	34.6	55.2
50–69	H3-1	69.2	65.4	47.4	56.8	59.1	16.7	48.2
	H3-2	57.0	13.5	24.3	54.9	39.3	36.8	38.9
	H3-3	55.5	38.7	41.3	68.6	51.0	44.4	49.7
	H3-4	8.0	45.5	35.5	64.8	34.1	31.3	33.8
	H3-5	30.8	30.0	20.7	54.5	35.0	19.7	32.5
	H3-6	27.8	31.2	46.8	77.7	44.2	21.2	41.6
70–80	H4-1	86.9	75.6	78.0	97.5	84.8	51.2	77.2
	H4-2	77.7	65.0	3.2	74.6	55.2	17.9	51.9
	H4-3	43.1	48.4	46.1	43.1	45.4	76.2	49.2
	H4-4	29.5	31.0	52.3	57.4	42.2	34.4	41.2
DHCM								
10–29	D1-1	99.5	38.0	99.8	99.5	94.7	29.6	85.2
	D1-2	26.2	8.6	44.8	32.7	28.3	5.8	23.6
30–49	D2-1	25.6	60.2	44.2	74.7	47.5	47.8	47.5
	D2-2	66.7	13.3	51.0	97.5	75.2	35.4	65.9
50–69	D3-1	22.9	8.0	28.5	22.5	18.4	8.3	16.1
	D3-2	69.2	36.5	66.9	94.3	61.0	90.7	65.2
	D3-3	49.3	60.4	0.1	28.5	42.9	48.2	44.2
	D3-4	90.3	91.5	36.9	56.5	73.7	48.7	69.8
	D3-5	98.1	99.8	83.6	33.1	76.1	76.2	74.8
	D3-6	30.3	34.2	26.3	75.1	39.3	58.1	40.9
	D3-7	35.2	65.2	35.3	91.4	56.7	74.5	58.7
	D3-8	44.8	47.0	51.7	80.1	61.8	0.1	53.2

B. Percentage area of myocardial disarray (%)

	HCM				DHCM		
	H1	H2	H3	H4	D1	D2	D3
Age group (yr)	10–29	30–49	50–69	70–80	10–29	30–49	50–69
Number of patients	2	2	6	4	2	2	8
Mean±SD	50.2±21.9	54.0±1.8	40.8±7.2	54.9±15.6	54.4±43.6	56.7±13.0	52.9±19.0

Abbreviations as in Tables 1, 2.

fibrosis of DHCM would be within 10%. Autopsy reports of HCM have revealed that some of these patients died from congestive heart failure, which was thought to be included in their natural course. Nowadays, autopsy findings indicate that dilatation of the left ventricle in patients who died of congestive heart failure is a consequence of the natural course[1,11–13]. According to Yutani *et al.*[6], cardiac

failure in the clinical course of HCM might be due to massive fibrosis of the left ventricle. We compared the percentage area of myocardial fibrosis and disarray between HCM and DHCM hearts to clarify the natural course of HCM and determine whether DHCM is included in the natural course of HCM.

In the total evaluation of both ventricles, each age group of the HCM cases showed < 10% area of myocardial fibrosis and a gradual increase with age, whereas the DHCM cases had over 20% area of myocardial fibrosis. Furthermore, this fibrosis of the DHCM cases was diffuse and never progressed with increased age, suggesting that the percentage areas of disarray and fibrosis in DHCM are broader and much higher than those of HCM. Therefore, the massive fibrosis of DHCM may simply be the result of the broader area of disarray, so this particular type of DHCM is different from the natural course of other factor-affected HCM (*e.g.*, inflammation or ischemia). From the standpoint of morphological pathogenesis, the disease process in DHCM might be different from that in HCM.

The pathogenesis different of characteristically broad and diffuse fibrosis in patients with HCM has been debated[1,11-13]. In these studies, spasm, hypoxia, hypotension, and metabolic disorders were mentioned, but the mechanism of the pathogenesis of the fibrosis in HCM is not yet fully understood.

Dilated phase of hypertrophic cardiomyopathy prediction

It is difficult to distinguish DHCM from HCM at the onset by clinical and pathological findings. We have experienced patients with DHCM who showed progression to dilatation of the left ventricle and died of congestive heart failure, resembling DCM. There are some patients with this type of DHCM who show early onset and rapid progression and poor prognosis, and others who demonstrate adult onset and relatively slow progression[7]. These findings suggest that the genetic abnormalities previously reported do not completely explain the correlation between genetic abnormalities and morphogenesis or clinical severerity[14]. These findings emphasize the role of other factors.

We suggest that if cardiac myocytes have no severe abnormalities of sarcomeric protein, an abnormal construction might induce slight fibrosis mediated by activation of extracellular matrix, and this fibrosis would increase with age. Severe (including DHCM) cases might have a disturbance in a more important portion of the functional sites of sarcomeric proteins.

The difference of the pathogenesis and prognosis for HCM and DHCM patients could depend on the disturbance of sarcomeric proteins and additional abnormalities which include more important components of the cytoskeletons.

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要　約

肥大型心筋症と拡張相肥大型心筋症における心筋線維化面積率と心筋錯綜配列面積率の比較検討

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肥大型心筋症(HCM)と肥大型心筋症の経過中に左室の拡張をきたすいわゆる拡張相肥大型心筋症(DHCM)において，心筋線維化面積率と心筋錯綜配列面積率を比較することにより，肥大型心筋症の自然歴を明らかにし，更に拡張相肥大型心筋症がその自然歴に含まれるか否かについて検討した．

当センターにおいて病理解剖を行ったHCM症例14例，DHCM症例12例，合計26症例を対象に，各年代別に分類して検討した．方法は病理解剖により得られた乳頭筋付着部位における心横断面を病理形態学的に画像解析ソフトを用いて解析した．両心室ともに，HCM症例の全ての各年代群における心筋線維化面積率は10%以下であり，また年齢とともに緩徐な増加傾向を示した．一方，DHCM症例においてはいずれの年代群においても20%以上であり，瀰漫性の心筋線維化を示し，年齢に伴う増加傾向は認められなかった．また心筋錯綜配列面積率では，DHCM症例中3症例が

90%を超える高い心筋錯綜配列を示した.

以上の結果から，DHCMにおける心筋線維化面積率はHCMに比較し高く，かつHCMのような年齢とともに認められる緩徐な増加傾向は示さなかったことから，DHCMにおいては現在も明らかな病因論はなく，収縮蛋白レベルでの異常を含む，より広範囲に及ぶ心筋錯綜配列が瀰漫性の心筋線維化を惹起し，両病型間における心筋線維化面積率の差異をもたらしているものと考えられた.

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References

1) Maron BJ, Epstein SE: Hypertrophic cardiomyopathy: Recent observations regarding the specificity of three hallmarks of the disease: Asymmetric septal hypertrophy, septal disorganization and systolic anterior motion of the anterior mitral leaflet. Am J Cardiol 1980; **45**: 141-154
2) Davies MJ, Pomerance A, Teare RD: Pathological features of hypertrophic obstructive cardiomyopathy. J Clin Pathol 1974; **27**: 529-535
3) Pomerance A, Davies MJ: Pathological features of hypertrophic obstructive cardiomyopathy (HOCM) in the elderly. Br Heart J 1975; **37**: 305-312
4) McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J: Prognosis in hypertrophic cardiomyopathy: Role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981; **47**: 532-538
5) ten Cate FJ, Roelandt J: Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. Am Heart J 1979; **97**: 762-765
6) Yutani C, Imakita M, Ishibashi-Ueda H, Hatanaka K, Nagata S, Sakakibara H, Nimura Y: Three autopsy cases of progression to left ventricular dilatation in patients with hypertrophic cardiomyopathy. Am Heart J 1985; **109**: 545-553
7) Nagata S, Park YD, Minamikawa T, Yutani C, Kamiya T, Nishimura T, Kozuka T, Sakakibara H, Nimura Y: Thallium perfusion and cardiac enzyme abnormalities in patients with familial hypertrophic cardiomyopathy. Am Heart J 1985; **109**: 1317-1322
8) Roberts WC, Ferrans VJ: Pathologic anatomy of the cardiomyopathies: Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. Hum Pathol 1975; **6**: 287-342
9) Anderson KR, Sutton MG St J, Lie JT: Histopathological types of cardiac fibrosis in myocardial disease. J Pathol 1979; **128**: 79-85
10) Ferrans VJ, McAllister HA Jr, Haese WH: Infantile cardiomyopathy with histiocytoid change in cardiac muscle cells: Report of six patients. Circulation 1976; **53**: 708-719
11) Maron BJ, Tajik AJ, Ruttenberg HD, Graham TP, Atwood GF, Victorica BE, Lie JT, Roberts WC: Hypertrophic cardiomyopathy in infants: Clinical features and natural history. Circulation 1982; **65**: 7-17
12) Maron BJ, Wolfson JK, Epstein SE, Roberts WC: Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986; **8**: 545-557
13) Maron BJ, Wolfson JK, Roberts WC: Relation between extent of cardiac muscle cell disorganization and left ventricular wall thickness in hypertrophic cardiomyopathy. Am J Cardiol 1992; **70**: 785-790
14) Straceski AJ, Geisterfer-Lowrance A, Seidman CE, Seidman JG, Leinwand LA: Functional analysis of myosin missense mutations in familial hypertrophic cardiomyopathy. Proc Natl Acad Sci USA 1994; **91**: 589-593