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High Prevalence of Atrial Fibrosis in Patients With Dilated Cardiomyopathy

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Objectives. **We examined the extent of fibrotic changes in the left atrium of cardiomyopathic human hearts and investigated the relation of mechanical overload caused by left ventricular dysfunction to fibrosis of the left atrium.**

Background. **Left atrial dysfunction in dilated cardiomyopathy may contribute to progression of heart failure. In contrast to fibrosis of the left ventricle, atrial fibrosis has not been extensively studied in cardiomyopathic hearts.**

Methods. **The extent of fibrosis in the left atrium and left ventricle was determined by an automatic image analyzer in 38 autopsied hearts obtained from 9 patients who died of noncardiac illness (control group), 16 patients with dilated cardiomyopathy, 6 patients with hypertrophic cardiomyopathy with features mimicking dilated cardiomyopathy and 7 patients with a previous myocardial infarction. Transverse sections were obtained at the upper margins of the foramen ovale and left auricle in the left atrium and the median level of the left ventricle.**

Results. **There were no significant differences in extent of left atrial dilation, left ventricular dysfunction or duration of illness among the three groups with cardiac disease. Percent area of left atrial fibrosis (mean ± SD) was significantly greater in the specimens from patients with dilated cardiomyopathy (13.1 ± 6.1%, $p < 0.01$) and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (26.5 ± 9.5%, $p < 0.01$) than in those from patients with an old myocardial infarction (3.8 ± 1.1%). Percent area of left ventricular fibrosis in hearts from patients with dilated cardiomyopathy (12.9 ± 8.6%) was significantly smaller than that in hearts from patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (35.8 ± 11.9%, $p < 0.01$) and a previous myocardial infarction (38.4 ± 8.0%, $p < 0.01$). Percent area of atrial fibrosis was significantly correlated with left ventricular ejection fraction in the group with a previous myocardial infarction but not in the other groups.**

Conclusions. **There was a high degree of fibrotic change in the left atrium in the groups with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy. Our findings suggest that atrial fibrosis in these patients may not have been related to mechanical overload of the left atrium but to some other, still unknown mechanisms.**

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Cardiac dilation and decreased contractile function are characteristic of dilated cardiomyopathy (1). Previous studies (2,3) have demonstrated that fibrosis of the ventricular wall is prominent in dilated cardiomyopathy; however, the correlation between the extent of fibrosis and contractile function is controversial. Fibrosis primarily contributes to the stiffness of the ventricular wall and thus may account for the elevated end-diastolic pressure of the left ventricle. In stiff, especially failing, hearts, left atrial systolic function may be important for ventricular filling during diastole (4,5), and atrial fibrillation or flutter can produce atrial failure, with severe detrimental effects on ventricular filling and on the overall pump function of the heart (6,7). Triposkiadis et al. (8) reported that depression of left atrial contractile function was significantly greater in patients with dilated cardiomyopathy than in those with aortic valve disease with comparable left ventricular dysfunction. However, left atrial tissue from cardiomyopathic hearts has not undergone extensive histologic study (9–14).

In the present study, we investigated the extent of left atrial fibrosis in autopsied hearts from patients with dilated cardiomyopathy and hypertrophic cardiomyopathy with features mimicking dilated cardiomyopathy. In an attempt to clarify the effect of mechanical overload on atrial fibrosis, we also studied the extent of atrial fibrosis in hearts from patients with a previous myocardial infarction with left ventricular dysfunction comparable to that seen in cardiomyopathy.

Methods

Materials. We studied 38 autopsied hearts: 9 from patients who died of noncardiac illness (control group [5 men, 4 women]); 6 from patients with hypertrophic cardiomyopathy

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Table 1. Clinical and Pathologic Features of 38 Autopsied Hearts

Case No.	Age (yr)/ Gender	Heart Weight (g)	Wall Thickness (mm)			LV Fibrosis (%)	LA Fibrosis (%)
			LA FW	LV FW	LVS		
Hypertrophic Cardiomyopathy Mimicking Dilated Cardiomyopathy							
1	18/M	900	2.1	11	18	18.6	44.8
2	47/F	500	1.8	10	19	30.9	21.6
3	17/F	420	2.0	11	9	29.9	16.6
4	21/F	530	2.7	12	21	45.7	32.4
5	49/F	750	2.5	14	22	51.5	20.8
6	21/M	780	2.1	3	7	38.1	22.5
Mean	29	647	2.2	10	16	35.8	26.5
±SD	±14*	±173	±0.3	±4	±6	±11.9†	±9.5‡
Dilated Cardiomyopathy							
1	36/F	500	1.7	10	10	9.6	4.4
2	51/M	550	2.6	9	10	5.9	5.0
3	51/M	480	2.1	6	9	4.7	16.4
4	42/M	480	1.6	10	6	11.3	23.6
5	63/M	450	2.2	8	10	31.6	21.0
6	46/M	600	2.1	11	11	15.6	12.6
7	40/M	390	2.7	11	12	23.5	12.7
8	36/F	500	1.7	5	6	11.3	13.0
9	23/M	560	2.4	11	10	16.7	19.6
10	72/M	610	2.1	11	10	4.9	17.7
11	48/M	405	2.2	8	9	11.8	19.7
12	64/M	540	2.0	10	9	0.6	10.5
13	67/M	590	1.9	10	11	14.4	11.9
14	65/M	510	1.7	10	11	13.8	12.5
15	37/F	530	2.3	8	8	3.8	4.5
16	49/M	940	2.1	11	13	26.9	3.9
Mean	49	538	2.1	9	10	12.9	13.1
±SD	±13	±117	±0.3	±2	±2	±8.6	±6.1§

	Age (yr)	Heart Weight (g)	LA Wall Thickness (mm)	LV Fibrosis (%)	LA Fibrosis (%)
Previous Myocardial Infarction (n = 7 [6M/1F])					
Range	47–75	400–570	1.6–2.6	24.4–51.6	1.9–5.5
Mean ± SD	59 ± 9	453 ± 54	2.1 ± 0.4	38.4 ± 8.0‡	3.8 ± 1.1
Control Group (n = 9 [5M/4F])					
Range	43–66	230–310	2.9–3.4	0.4–1.4	0.8–1.8
Mean ± SD	53 ± 9	286 ± 29	3.1 ± 0.1	0.9 ± 0.3	1.4 ± 0.3

*$p < 0.05$ versus old myocardial infarction. †$p < 0.01$ versus dilated cardiomyopathy. ‡$p < 0.01$ versus dilated cardiomyopathy and old myocardial infarction. §$p < 0.01$ versus old myocardial infarction. F = female; FW = free wall; LA = left atrial; LV = left ventricular; LVS = left ventricular septum; M = male.

mimicking dilated cardiomyopathy (2 men, 4 women); 16 from patients with dilated cardiomyopathy (13 men, 3 women); and 7 from patients with a previous myocardial infarction (6 men, 1 woman) (Table 1).

Hypertrophic cardiomyopathy mimicking dilated cardiomyopathy is a form of hypertrophic cardiomyopathy characterized by progressive dilation of the left ventricle in the late stage (14–17). The diagnosis of hypertrophic cardiomyopathy mimicking dilated cardiomyopathy was made according to previously described criteria (18). In three of the six patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, progression from typical hypertrophic cardiomyopathy to dilated cardiomyopathy-like features was detected by echocardiography. In the remaining three patients, dilated cardiomyopathy was diagnosed on the basis of clinical features, but autopsy showed extensive myocardial fiber disarray distributed mainly in the ventricular septum. Thus, hypertrophic cardiomyopathy was diagnosed on the basis of histologic findings. This diagnosis was also supported by a familial prevalence of hypertrophic cardiomyopathy.

The clinical diagnosis of dilated cardiomyopathy was based on the criteria of the World Health Organization (19) for the

definition and classification of cardiomyopathies. No diffuse disarray of myocytes or marked asymmetric ventricular hypertrophy was observed in specimens from patients with dilated cardiomyopathy. A familial prevalence of dilated cardiomyopathy was observed in two patients.

The mean age of the patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy was significantly younger than that of patients in the other two groups ($p < 0.01$ vs. patients with dilated cardiomyopathy and those with an old myocardial infarction). All patients died of severe congestive heart failure. No cases of sudden death were included in the present study. Mean heart weight was significantly greater in the patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy than in those with dilated cardiomyopathy ($p < 0.05$). Mean ratio of septal/free wall thickness was 1.1 in the group with dilated cardiomyopathy and 1.6 in that with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy. The left atrial wall was thin in the three groups with cardiac disease compared with the control group ($p < 0.05$); there was no significant difference in thickness among the three groups with cardiac disease (Table 1).

Lumen diameter of the extramural coronary arteries was <50% in the groups with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy and dilated cardiomyopathy. In the group with myocardial infarction, three patients had triple-vessel disease, three had proximal left anterior descending coronary artery disease, and one had left circumflex coronary artery disease. All patients had anterior or lateral myocardial infarction, or both. They died of incurable severe congestive heart failure in the chronic stage. There was no significant coronary lumen narrowing in the control group.

Histologic examination. *Left ventricle.* The hearts were weighed and fixed in 10% formalin and sectioned transversely from base to apex at 1-cm intervals. A slice from the midlevel of the autopsied heart was embedded in paraffin. The whole sectioned surface was cut into sections ~5-μm thick on a glass slide and stained with hematoxylin-eosin and Masson's trichrome. Each tissue section was divided into anterior, lateral, posterior and septal regions.

Left atrium. After fixation, transverse sections were cut from the area just above the left auricle and foramen ovale (Fig. 1). After staining with hematoxylin-eosin and Masson's trichrome, each section was divided into anterior, lateral, posterior and septal regions.

The 5-μm thick preparations stained with Masson's trichrome were enlarged 10 times with a photographic enlarger. Areas that stained blue, indicating fibrosis, were carefully traced with a fine black pen. The percent area of fibrosis was measured with an automatic image processing system (Olympus Vip-21), as previously described (20,21).

The percent area of fibrosis in the entire ventricular and atrial wall of the transverse slice was obtained by dividing the total area of fibrosis by the total tissue area. To determine the intramural distribution of fibrosis, the regional percent area of fibrosis in the anterior, lateral, posterior and septal walls of the left atrium and left ventricle was calculated separately. Papillary muscles were excluded from measurement of fibrosis in the ventricular section. Endocardium and epicardium were excluded from measurement of fibrosis in the atrial section.

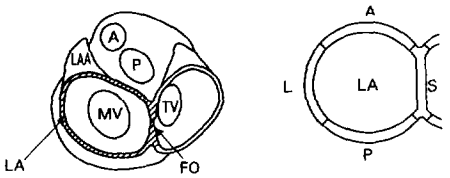

Figure 1. Left, Transverse sections obtained from area just above the left auricle (LAA) and foramen ovale (FO). A = aorta; LA = left atrium; MV = mitral valve; P = pulmonary artery; TV = tricuspid valve. **Right,** Schematic diagram of transverse section of the left atrial (LA) wall, divided into anterior (A), lateral (L), posterior (P) and septal (S) regions.

To confirm the accuracy of measurements, we analyzed the extent of fibrosis in two transverse sections obtained at ~10-mm intervals from two hearts in each group. In all cases, fibrosis was traced and quantified independently by two morphologists. Measurements varied by <7%.

Hemodynamic measurements. Hemodynamic measurements determined by cardiac catheterization, contrast or radionuclide left ventriculography and Doppler echocardiography (22) were obtained within 3 months of death. We defined the duration of illness as the period from the first episode of severe congestive heart failure (New York Heart Association functional class III) to death. The duration of illness was not significantly different among groups. There were also no significant differences in ejection fraction or mitral regurgitation grade. Left ventricular end-diastolic dimension in the group with dilated cardiomyopathy was significantly larger than that in the groups with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy and previous myocardial infarction ($p < 0.05$, respectively). Left atrial dimension and mean pulmonary artery wedge pressure did not differ among groups (Table 2). The incidence of atrial fibrillation was 33% in the group with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, 12.5% in the group with dilated cardiomyopathy and 14% in the group with a previous myocardial infarction.

Statistical analysis. Data are expressed as mean value ± SD. Because of the large variance of differences in each group, nonparametric methods (Wilcoxon test with Bonferroni procedure) were used when appropriate; $p < 0.05$ was considered statistically significant.

Results

Left atrial microscopic findings. Figure 2 (top) shows a microscopic specimen from the left atrium of a patient with an old myocardial infarction. In control hearts and in those from patients with a previous myocardial infarction, fibrous tissue extending from the perivascular fibrosis was rarely observed around the well defined muscle bundles. The extent of fibrosis was minimal, and the myocardium showed no particular

Table 2. Clinical Course and Hemodynamic Data

Study Group	Family History (+/−)	Duration of Illness (mo)	Echocardiographic Data		FS (%)	mPAWP (mm Hg)	EF (%)	MR
			LVDd (mm)	LAD (mm)				
DCM-like HCM (n = 6)	5/1	32 ± 14	60 ± 7*	39 ± 12	13.5 ± 5.4	22 ± 9 (n = 5)	20 ± 3 (n = 5)	2.0 ± 0.6
DCM (n = 16)	2/14	34 ± 19	70 ± 8	43 ± 9	13.1 ± 5.3	18 ± 9 (n = 14)	23 ± 6 (n = 15)	2.1 ± 1.1
OMI (n = 7)	—	29 ± 16	59 ± 8*	40 ± 7	15.6 ± 11.7	25 ± 5	27 ± 9 (n = 6)	1.3 ± 1.2

*$p < 0.05$ versus dilated cardiomyopathy (DCM). DCM-like HCM = hypertrophic cardiomyopathy with features mimicking dilated cardiomyopathy; Duration of illness = period from functional class III episode to death; EF = ejection fraction; FS = fractional shortening; LAD = left atrial dimension; LVDd = left ventricular end-diastolic dimension; mPAWP = mean pulmonary artery wedge pressure; MR = mitral regurgitation (grade 0–4); OMI = old myocardial infarction; + = presence; − = absence.

changes. In hearts with dilated cardiomyopathy, there was a diffuse netlike fibrosis within the muscle bundles, with moderate disruption of bundle structure. The muscle mass was relatively well preserved, but some myocardial fibers showed vacuolar degeneration and a combination of hypertrophy and attenuation (Fig. 2, middle). In contrast, massive fibrosis and marked loss of muscle mass were observed in the left atrium of hearts with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (Fig. 2, bottom). Muscle bundles were markedly disrupted or associated with unrecognizable structures with occasional vacuolar degeneration and myocardial attenuation, or both. Almost complete replacement with fibrous tissue was seen in the center of the fibrotic area.

The percent area of fibrosis in a transverse section of the entire left atrium was 1.4 ± 0.3% in control hearts, 26.5 ± 9.5% in hearts with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, 13.1 ± 6.1% in hearts with dilated cardiomyopathy and 3.8 ± 1.1% in those with a previous myocardial infarction, significantly greater in hearts with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy than in those with dilated cardiomyopathy ($p < 0.01$) and a previous myocardial infarction ($p < 0.01$) and significantly greater in hearts with dilated cardiomyopathy than in those with a previous myocardial infarction ($p < 0.01$) (Table 1, Fig. 3).

None of the groups showed any significant regional variation in the extent of fibrosis (Fig. 4).

Percent area of left ventricular fibrosis. The percent area of all left ventricular fibrosis in hearts with dilated cardiomyopathy (12.9 ± 8.6%) was significantly smaller than that in hearts with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (35.8 ± 11.9%, $p < 0.01$) and a previous myocardial infarction (38.4 ± 8.0%, $p < 0.01$). There was no significant regional variation in extent of fibrosis in hearts with dilated cardiomyopathy and hearts with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy. Percent area of left ventricular fibrosis did not correlate with that in the left atrium in either group.

Relation of percent area of left atrial fibrosis to ejection fraction. Extent of left atrial fibrosis was significantly correlated with left ventricular ejection fraction ($r = -0.82$, $p < 0.05$) in hearts with an old myocardial infarction. No correlation between extent of fibrosis and ejection fraction was observed in the other groups (Fig. 5). Because the number of patients with chronic atrial fibrillation was small, we could not detect any trend in the relation of these two variables in patients with versus without sinus rhythm.

Discussion

Histologic assessment of atrial fibrosis. Previous studies of atrial fibrosis were limited with regard to quantitative assessment of extent of fibrotic changes (e.g., tissue samples that were too small and sampling sites that were limited to the endocardium [23] or atrial appendage [24]). Bailey et al. (25) observed extensive atrial tissue fibrosis in patients with chronic atrial fibrillation, but this may lead to an incorrect quantitative correlation between extent of fibrotic changes and duration of atrial fibrillation because biopsied tissue samples may not reflect histologic changes in the entire atrium. Histologic examination of entire transverse sections is necessary to evaluate the distribution and extent of fibrosis of the myocardium. To our knowledge, the present study is the first to quantitatively assess the extent of fibrosis on transverse slices of the entire left atrium using an automatic image analyzer. We tested the reliability of using percent fibrosis as an index of the extent of fibrotic changes in the whole atrium by comparing the percent fibrosis in two transverse slices obtained at 10-mm intervals from two hearts in each group. Percent fibrosis was comparable in tissue slices obtained from the same heart, suggesting that the percent fibrosis observed in the transverse slice of the atrium represented the extent of fibrotic changes in the whole atrium. We also confirmed that our measurements of fibrosis were reproducible in the present study. Thus, percent fibrosis appeared to be a reliable index of fibrotic changes in atrial tissue.

Fibrosis of the left atrial wall. Aging and mechanical overload are believed to be two major causes of fibrosis in the left atrium. The distribution of fibrosis and adipose tissue in the atrial wall has been found to increase with age, whereas the proportion of muscle fibers decreases (26). In the present

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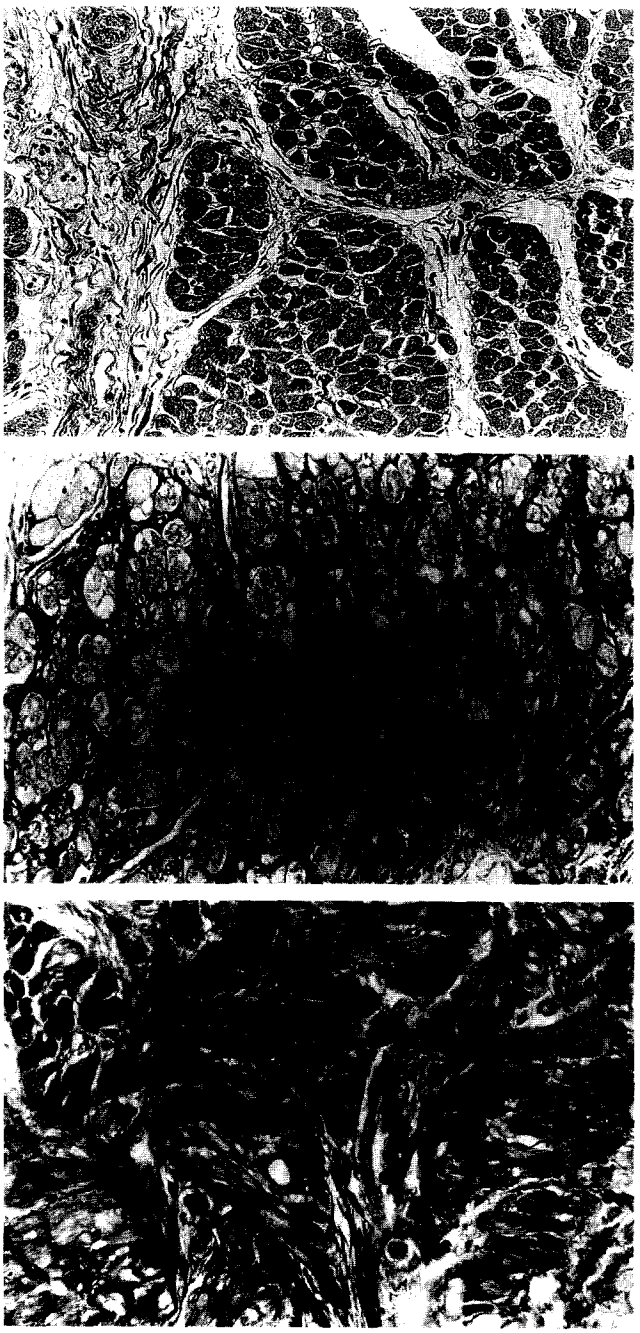

Figure 2. Left atrial wall specimens from **(top)** a patient with an old myocardial infarction showing perivascular fibrosis and compact myocardium in muscle bundles; **middle** a patient with dilated cardiomyopathy showing severe interstitial fibrosis and moderate muscle bundle disruption; and **bottom** a patient with hypertrophic cardiomyopathy with features mimicking dilated cardiomyopathy showing complete replacement fibrosis and marked muscle bundle disruption. Hematoxylin-eosin and Masson's trichrome stain, ×170, reduced by 30%.

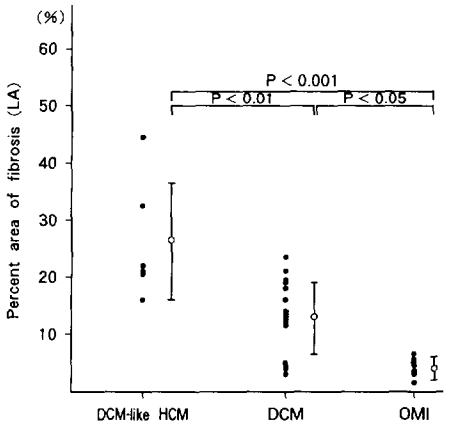

Figure 3. Percent area of left atrial (LA) fibrosis in DCM-like HCM = hypertrophic cardiomyopathy with features mimicking dilated cardiomyopathy; DCM = dilated cardiomyopathy; OMI = old myocardial infarction. **Vertical bars and open circles** = mean ± SD.

study, patients with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy were much younger than those with an old myocardial infarction. However, percent fibrosis was significantly greater in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy than in those with a previous myocardial infarction, suggesting that the marked fibrosis in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy may be related to factors other than aging. Mechanical overload may account primarily for fibrosis of atrial tissue. Triposkiadis et al. (8) reported that left atrial systolic function is more impaired in patients with dilated cardiomyopathy than in those with left ventricular dysfunction caused by valvular abnormalities, despite comparable mechanical loads to the atrium in both diseases. This finding suggests that mechanical overload itself does not cause marked fibrotic changes in the atrium. This hypothesis is supported by the findings of Bailey et al. (25), who observed minimal fibrotic changes in the left atrium in patients with nonrheumatic mitral valvular abnormalities, such as idiopathic cardiomyopathy and papillary muscle dysfunction. In our study, there was a close correlation between left ventricular ejection fraction and percent area of atrial fibrosis in patients with an old myocardial infarction. Although we did not determine left atrial pressures in our patients, it is possible that the mechanical load of the left atrium may be inversely correlated with left ventricular ejection fraction. If so, the extent of atrial fibrosis in the group with an old myocardial infarction may reflect the mechanical load of the atrial muscle. However, the load-dependent fibrotic changes in the group with an old myocardial infarction were significantly smaller than those observed in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, indicating that causes other than mechanical overload may be primarily responsible for fibrotic changes in idiopathic myopathy.

Unrecognized viral myocarditis may be an underlying cause of dilated cardiomyopathy in a substantially large number of patients (27). Bowles et al. (28) reported that Coxsackie B virus RNA was frequently observed in biopsied ventricular tissue samples from patients with dilated cardiomyopathy. Matsumori et al. (29) also reported that viral myocarditis

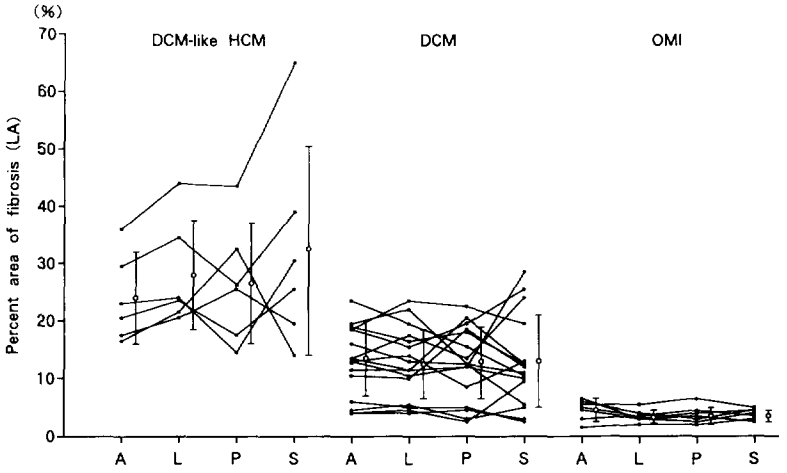

Figure 4. Regional distribution of left atrial (LA) fibrosis. **Vertical bars and open circles** = mean ± SD. Abbreviations as in Figures 1 and 3.

occurred in both the atrium and ventricle in an experimental animal model. Thus, it is likely that the marked fibrotic changes in patients with idiopathic cardiomyopathy are related, in part, to previous viral myocarditis. Although there was no correlation between fibrotic changes in the ventricle and atrium in individual patients, the high prevalence of myocardial fibrosis observed in patients with idiopathic cardiomyopathy strongly supports this hypothesis.

Fibrosis in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy mimicking dilated cardiomyopathy. Percent fibrosis of the left ventricle was significantly higher in patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy than in those with dilated cardiomyopathy (35.8% vs. 12.9%, $p < 0.01$) despite comparable left ventricular ejection fractions and intervals from the development of heart failure symptoms to death. Our findings in patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy are consistent with those previously reported (14). A previous study (30) suggested that the transition from hypertrophic cardiomyopathy to hypertrophic cardiomyopathy mimicking dilated cardiomyopathy is accompanied by an increase in ventricular fibrosis. Spirito et al. (31) reported that 5% to 10% of patients with hypertrophic cardiomyopathy show progressive thinning of the left ventricular wall and dilation of the left ventricular cavity. This phenomenon has been classified as hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (18), which is characterized by extensive left ventricular myocardial fibrosis. Our findings in the hearts from the group with an old myocardial infarction suggest that fibrotic change itself does not cause ventricular dilation, that is, remodeling of the left ventricle. In cardiomyopathic Syrian hamsters, left ventricular dilation and wall thinning were associated with increased collagenase activity. This degradation of collagen may have caused remodeling of the ventricle (32). Such a biochemical mechanism may be present in patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, although there is no direct evidence to support this hypothesis.

Myocardial ischemia may also be responsible for the transition from hypertrophic cardiomyopathy to hypertrophic cardiomyopathy mimicking dilated cardiomyopathy because abnormal myocardial structures, such as disarray (14,18,31,33,34), can impair the coronary microvascular vasodilatory response (35). However, this hypothesis may not be plausible in the atrium because the atrial chamber, which is like a low pressure reservoir, is not susceptible to ischemia. Atrial infarction is extremely rare (36,37). In the present study, three patients with an old myocardial infarction had complete obstruction of the sinus node and atrial circumflex arteries in the left atrium. However, none of these patients had signs of left atrial infarction, and atrial fibrosis was minimal. There is often a family link in patients who progress from hypertrophic cardiomyopathy to hypertrophic cardiomyopathy mimicking dilated cardiomyopathy (14), suggesting that genetic factors may be involved. The tissue renin-angiotensin system and growth factors, such as transforming growth factor-beta$_1$ and basic fibrinogen growth factor and cytokines may also play a major role in both ventricular and atrial fibrosis, although we observed no correlation between ventricular and atrial fibrosis. Sympathetic activity may also modulate these processes (38). Investigation of neurohormonal and immunologic alterations in hypertrophic cardiomyopathy mimicking dilated cardiomyopathy is needed to clarify the underlying mechanism of myocardial fibrosis.

Limitation of the study. A major limitation of this study is that we examined autopsied hearts, and, thus, the present results may represent histologic changes in severely ill patients only. However, the mean percent area of fibrosis in the ventricle in patients with dilated cardiomyopathy (12.9 ± 8.6%) was consistent with that found in previous studies based on biopsied samples, indicating that the population bias may not be excessively large.

The hemodynamic data in the present study were obtained within 3 months of death, and pulmonary artery wedge pressures were obtained within 6 months of death, complicating the relation between hemodynamic data and histologic changes at autopsy. However, the interval between the hemodynamic and

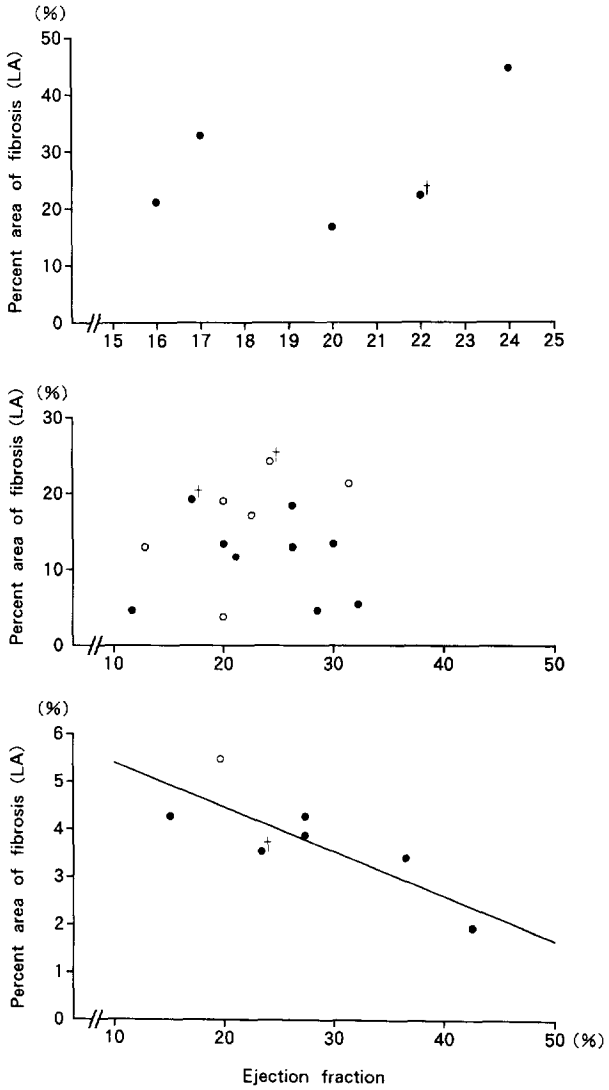

Figure 5. Relation of percent area of left atrial (LA) fibrosis to left ventricular ejection fraction in patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy **(top)** ($r = -0.815$, p = NS); dilated cardiomyopathy **(middle)** ($r = 0.516$, p = NS); and an old myocardial infarction **(bottom)** ($r = -0.815$, $p < 0.05$). **Solid circles** = mitral regurgitation grade 1 to 2; **open circles** = mitral regurgitation grade 3 to 4. †Chronic atrial fibrillation.

the autopsy studies was comparable among the three study groups, and, thus, the difference among groups may be minimal. We could not reach any conclusion as to whether atrial fibrosis increases the incidince of atrial fibrillation because the number of patients with chronic atrial fibrillation was minimal. Nevertheless, the incidence of atrial fibrillation was highest in patients with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy, indicating that extensive atrial fibrosis may increase the incidence of nonsinus atrial rhythm. Despite these limitations, to our knowledge the present study is the first to demonstrate a high prevalence of atrial fibrosis in patients with dilated cardiomyopathy, especially those with hypertrophic cardiomyopathy mimicking dilated cardiomyopathy.

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