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Histopathological specificity of hypertrophic obstructive cardiomyopathy

*Myocardial fibre disarray and myocardial fibrosis**

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SUMMARY The topography and specificity of fibre disarray and fibrosis in hypertrophic obstructive cardiomyopathy were determined in a histological study comprising 40 necropsy hearts—10 with hypertrophic cardiomyopathy, 10 with congestive cardiomyopathy, 10 with aortic valve stenosis, and 10 normal hearts. Seven standard regional sections were sampled from each heart and graded "double-blind" (tissue location and disease entity) for severity and extent of fibre disarray and four distinct types of myocardial fibrosis. Statistical comparison of the severity and distribution of indices of fibre disarray and fibrosis within each group and between the normal and the disease groups showed that fibre disarray and fibrosis were qualitatively non-specific for hypertrophic cardiomyopathy. However, when fibre disarray was quantified (1) it was significantly increased in hypertrophic cardiomyopathy and allowed separation of hearts with hypertrophic cardiomyopathy from normal hearts and from those with congestive cardiomyopathy and aortic stenosis, (2) it did not vary significantly among sections of the left ventricle (that is, between the septum and the free wall) in hypertrophic cardiomyopathy, (3) it was closely associated with plexiform fibrosis, and (4) it varied independently of wall and septal thickness. Though the histogenesis of fibre disarray is unknown, it probably represents an exaggeration of a non-specific common pathway for many diverse pathophysiological processes.

Since the early descriptions of hypertrophic obstructive cardiomyopathy by Teare[1] and Brock,[2] this clinical disorder has been diagnosed at the bedside by the presence of a sharp carotid upstroke, a high-frequency systolic murmur, and a hyperdynamic apical impulse[3–5]; at cardiac catheterisation by the presence of a left ventricular outflow tract gradient at rest or on provocation[3–7]; on the echocardiogram by the presence of asymmetric septal hypertrophy[8–10] and systolic anterior motion of the mitral valve[11]; and pathologically by the myocardial fibre disarray and fibrosis in the disproportionately thickened interventricular septum.[1 12–15]

Recently, the specificity of echocardiographic features of hypertrophic cardiomyopathy has been seriously questioned.[16 17] Similarly, septal fibre disarray, initially thought to be pathognomonic of hypertrophic cardiomyopathy,[1 13 14] has been found to be present in normal hearts,[18 19] in many congenital malformations—particularly those in which the pattern of contraction is abnormal[20]—and also in animals after chronic endocardial pacing.[21]

Hitherto, there has been no systematic attempt to quantify the severity and distribution of fibre disarray and fibrosis in the transverse and longitudinal axes of the right and left ventricles in hypertrophic cardiomyopathy. We undertook such an evaluation (1) to investigate the specificity of fibre disarray as a histological marker in hyper-

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Table 1 *Sex, age, and heart weights in four groups: Normal, hypertrophic (obstructive) cardiomyopathy (HOCM), congestive cardiomyopathy (COCM), and aortic stenosis (AS)*

Group	No. of hearts	Sex		Age, mean (range) (y)	Heart weight (g)
		F	M		
Normal	10	6	4	43·3 (21–54)	324 (280–380)
HOCM	10	5	5	48·4 (14–72)	587 (300–830)
COCM	10	3	7	50·6 (40–81)	548 (400–760)
AS	10	3	7	71·5 (28–89)	532 (300–770)

trophic cardiomyopathy, (2) to determine whether there was a relation between fibre disarray and fibrosis and left ventricular hypertrophy, and (3) to study whether variation in the severity and distribution of fibre disarray and fibrosis might account for the variation in left ventricular function demonstrable both echocardiographically[22 23] and angiocardiographically.[24]

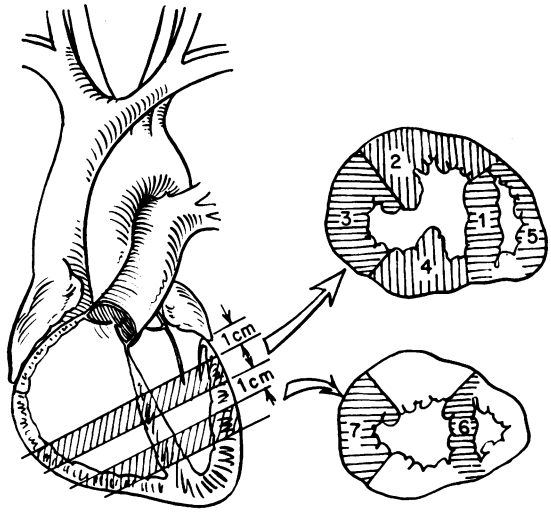

Fig. 1 *Two complete transverse segments were taken from each heart 1 cm and 3 cm below mitral valve annulus. Complete left and right ventricular walls and septum were represented in upper segment, and septum and lateral left ventricular wall in lower segment. Tissue blocks for histological study were taken from section locations 1 to 7. Section 1, upper septum; 2, anterior left ventricular wall; 3, upper lateral left ventricular wall; 4, posterior left ventricular wall; 5, right ventricular wall; 6, lower septum; and 7, lower lateral left ventricular wall.*

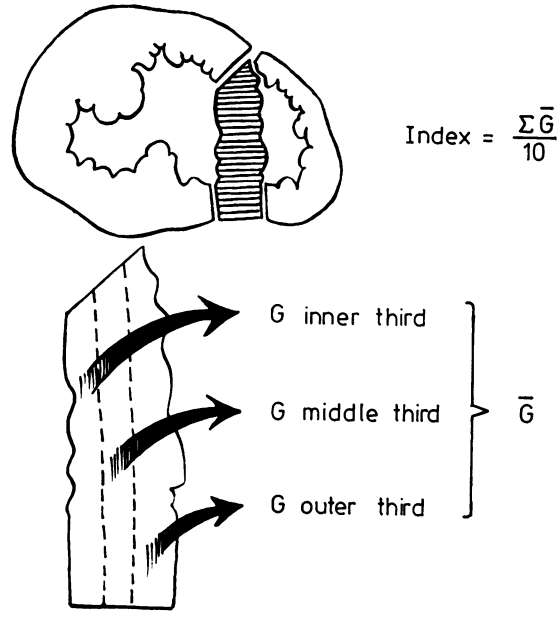

Fig. 2 *Tissue sections were divided into three regions, inner third, middle third, and outer third, with reference to left ventricular endocardial surface. Fibre disarray and each type of fibrosis were graded for each third* (G). *Score for section as a whole was expressed as a mean of three regions* ($\bar{G}$). *Numerical index for fibre disarray and each type of fibrosis was then obtained for each section locations 1 to 7 (Fig. 1) within each group (1 to 4) by dividing sum of mean grade of each section* ($\Sigma\bar{G}_1, \bar{G}_2 \ldots \bar{G}_{10}$) *by number of patients in each group (10).*

Materials and methods

A total of 40 necropsy hearts was studied. They comprised the following four groups, in none of which was there coronary artery stenosis with greater than 75 per cent cross-sectional luminal narrowing.

Group 1 consisted of 10 "normal" hearts from patients 21 to 54 years of age (mean 43 years) who had died from noncardiac causes. Group 2 consisted of 10 hearts from patients 14 to 72 years of age (mean 48 years) who had had a clinical diagnosis of hypertrophic cardiomyopathy and the concordant necropsy findings described by Davies *et al.*[25] and Roberts and Ferrans.[26] Group 3 consisted of 10 hearts from patients 40 to 81 years of age (mean 51 years) who had had idiopathic congestive cardiomyopathy with severely dilated ventricles. Group 4 consisted of 10 hearts from patients 28 to 89 years of age (mean 72 years) who had critical calcific aortic valve stenosis and severe left ventricular hypertrophy with similar heart weights and

wall thickness as the hearts with hypertrophic cardiomyopathy (Table 1).

The mean ages and sex distribution of the normal patients and those with hypertrophic and congestive cardiomyopathy (groups 1 to 3) were similar, but the mean age in patients with aortic stenosis (group 4) was greater; this difference reflects the different natural history of aortic stenosis. The means and ranges of the heart weights in the three disease groups (groups 2 to 4) were similar, and they were significantly greater ($p < 0{\cdot}01$) than those in the normal patients (group 1) (Table 1).

Tissue blocks for histological study were taken from each heart at two levels 1 cm and 3 cm below the mitral valve annulus (Fig. 1). The complete left and right ventricular walls and the septum were represented in the upper level, and the septum and the lateral left ventricular wall at the lower level (Fig. 1). Consecutive paraffin-embedded 5 μm tissue sections were stained with haematoxylin and eosin, elastic van Gieson, and Mallory-Heidenhain connective tissue stains. Each tissue section in locations 1 to 7 (Fig. 1) from the 40 hearts was assigned a random nonconsecutive number so that the two pathologists evaluating the severity of fibre disarray and fibrosis had no knowledge of the location of the tissue sample or of the group from which the tissue was obtained.

Tissue from each section location was divided into three regions—the inner third, middle third, and outer third, with reference to the left ventricular endocardial surface (Fig. 2). Fibre disarray and fibrosis were graded for each third, and the score for the section as a whole was expressed as a mean of three regions (Fig. 2).

Histologically, the presence or absence of fibre disarray in any given histological section was graded in ascending order of severity from 0 to 4 (Fig. 3). In grade 0 fibre disarray was not present. Grade 1 was assigned when 75 per cent or more of the area of the section showed muscle fibres characterised by normal side-branching fibres and parallel fibres in approximately equal proportions; in grade 2, side-branching muscle fibres were of approximately equal number to parallel fibres but occurred at a more obtuse angle than normal; in grade 3, in 50 to 75 per cent of the area of the section the apparent unidirectional nature of the myocardial fibres was lost because of formation of multiple orthogonal branches and incomplete whorls; and in grade 4, there was severe disruption of the normal orderly alignment of myocardial fibres, with complete and complex whorl formation.

Fibrosis was divided into four distinct types as follows (Fig. 4): (1) the term "microscopical scars" was used to describe foci of replacement fibrosis not discernible to the naked eye; (2) "interstitial fibrosis" refers to strands or bundles of collagenous connective tissue encircling or surrounding the individual myocardial fibres; (3) "perivascular fibrosis" refers to the condensation of collagenous connective tissue around intramural blood vessels, blending with the adventitia; and (4) "plexiform fibrosis" refers to a unique type of interstitial fibrosis seen in foci of myocardial fibre disarray in which fine and coarse bands of collagen, often with a wavy, "crimped" appearance, interlaced or enveloped the myocardial fibres.[27]

The severity of each histological type of myocardial fibrosis was also graded from 0 to 4 in ascending order of severity, in which grade 0 indicated not present. In addition, the transmural thickness (endocardial to endocardial, or endocardial to epicardial surface) of the tissue sections

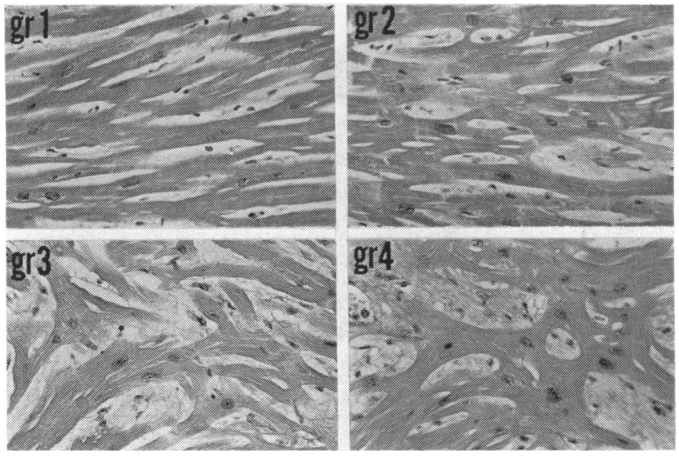

Fig. 3 *Histological grades (gr) of myocardial fibre disarray in ascending order of severity; grades 1 and 2 are normal variations but 3 and 4 represent true fibre disarray. (Haematoxylin and eosin. ×480.)*

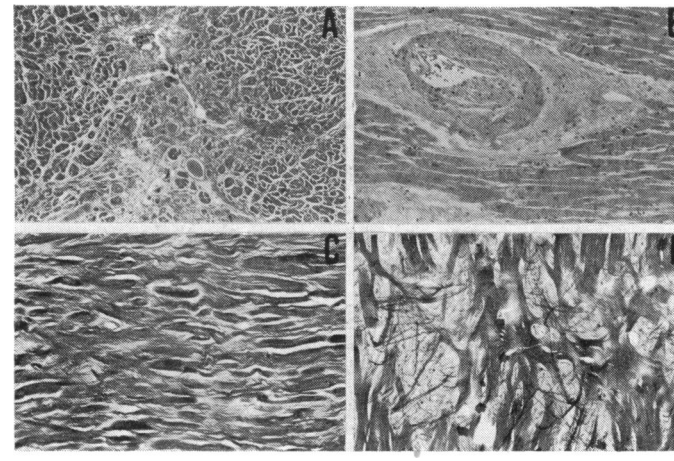

Fig. 4 *Representative photomicrographs of four histologically distinct types of myocardial fibrosis.*
A, *microscopical scars;*
B, *perivascular fibrosis;*
C, *interstitial fibrosis; and*
D, *plexiform fibrosis. (Mallory-Heidenhain. ×160.)*

was measured for each section location (1 to 7), and this was used as quantification of free wall and septal thickness, that is ventricular hypertrophy (Table 2).

When the grading of fibre disarray and individual types of fibrosis and the measurement of wall thickness of all sections had been completed, the observer double-blind (tissue location and disease entity) study code was broken and the histological slides were separated into the disease entity groups (four) and tissue-section locations (seven). A numerical index for fibre disarray and for each type of fibrosis was then obtained for each section location in each group by dividing the sum of the mean grade of each section by the number of patients in each group[9] (Fig. 2).

With the use of these indices of fibre disarray and fibrosis at each section location, not only was the severity of these factors assessed but the distribution of each was also evaluated throughout the transverse and longitudinal axes of the heart within each disease group. Subsequently, the severity and distribution of fibre disarray and fibrosis in aortic stenosis and hypertrophic and congestive cardiomyopathy were compared with normal and with one another. In addition, we investigated the relation between fibre disarray index, each type of fibrosis index, and wall thickness in the four groups.

Numerical data for each variable in all section locations 1 to 7 (Fig. 1) are given in Tables 2 to 7. (*Note:* in Fig. 5 and 7 to 10, for the purposes of clarity and simplicity, only sections 1 to 4 are shown, that is, all sections from the tissue slice taken 1 cm below the mitral annulus, because indices of fibre disarray and fibrosis from sections 6 and 7, taken from 3 cm below the mitral annulus, were not significantly different from those of sections 1 to 4 in each disease group and in the normal group.)

Statistical methods

For each diagnostic group and each index listed above, formal tests of significance were used to determine whether differences existed among sections of the heart. These tests, based on Hotelling's T^2,[28] are "overall" tests that considered all sections simultaneously. In general, such overall tests were followed by further paired comparisons of subgroups only when a statistically significant ($p < 0.05$) result was obtained.

In the absence of evidence of section differences for any of the indices, each index was summed over the six sections constituting the left ventricle for comparisons among diagnostic groups. Such comparisons, carried out separately for left and right ventricles, were based on one-way analysis of variance. This is an overall test that considered the four groups simultaneously. Paired comparisons were made only when the analysis of variance

Table 2 *Wall thickness for section locations 1 to 7 in the four groups studied**

Group	No. of hearts	Left ventricular wall thickness (mm) for each section location (Fig. 1) (Mean and SE)						Right ventricular wall thickness (mm)
		1	2	3	4	6	7	5
Normal	10	12·2 ±1·2	12·1 ±1·0	14·0 ±0·8	13·6 ±0·9	13·0 ±1·2	15·1 ±1·5	5·6 ±0·4
HOCM	10	20·6 ±1·9	20·4 ±2·2	20·8 ±1·5	17·5 ±1·3	22·5 ±1·8	19·9 ±1·3	7·9 ±0·6
COCM	10	7·5 ±0·7	13·5 ±1·0	12·8 ±0·9	12·0 ±1·0	14·7 ±1·1	12·9 ±1·9	6·7 ±0·5
AS	10	13·7 ±1·0	15·9 ±1·1	16·3 ±0·8	16·8 ±1·0	16·8 ±1·3	16·7 ±1·0	8·7 ±1·5

* Abbreviations as in Table 1.

indicated that a statistically significant difference existed.

As a test for association between wall thickness and index scores in the left ventricle, mean values (averaged over sections) were computed for each heart. Spearman's correlation coefficient (R_s) was then used to measure association. In addition, for determining whether fibre disarray and fibrosis index scores varied with wall thickness within individual hearts, R_s was computed separately for each heart and then averaged over the 10 subjects in each diagnostic group. This provided the basis for a two-tailed t test for association.

In all cases, differences that were not significant at the $p=0{\cdot}05$ level have been termed "not statistically significant".

Results

For the purposes of comparing the severity and distribution of fibre disarray in hypertrophic and congestive cardiomyopathy and aortic stenosis with normal, indices were derived for each section location in each disease group. The most severe involvement with fibre disarray would have an index of 4·0, whereas if fibre disarray was absent, the index would be zero. Indices numerically less than unity occurred when fibre disarray was present in a section location in some hearts and absent in other hearts within the same group.

FIBRE DISARRAY

Normal (group 1)

Fibre disarray occurred in normal hearts, as previously reported,[18 19] in the right and left ventricles. The fibre disarray index varied from 0·5 in the anterior left ventricular wall to 0·9 in the posterior left ventricular wall (Table 3, Fig. 5).

Table 3 *Fibre disarray index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	Fibre disarray index for each section location (Fig. 1) (Mean and SE)						
		Left ventricle						Right ventricle
		1	2	3	4	6	7	5
Normal	10	0·63 ±0·14	0·53 ±0·13	0·87 ±0·14	0·90 ±0·25	0·63 ±0·19	0·83 ±0·12	0·87 ±0·18
HOCM	10	1·93 ±0·13	1·50 ±0·22	1·43 ±0·13	1·10 ±0·14	1·53 ±0·20	1·30 ±0·20	0·97 ±0·15
COCM	10	0·80 ±0·21	0·77 ±0·21	0·77 ±0·17	0·77 ±0·16	0·67 ±0·17	1·20 ±0·19	0·97 ±0·24
AS	10	0·63 ±0·14	0·90 ±0·17	0·97 ±0·18	1·00 ±0·16	0·80 ±0·15	0·97 ±0·18	0·83 ±0·24

* Abbreviations as in Table 1.

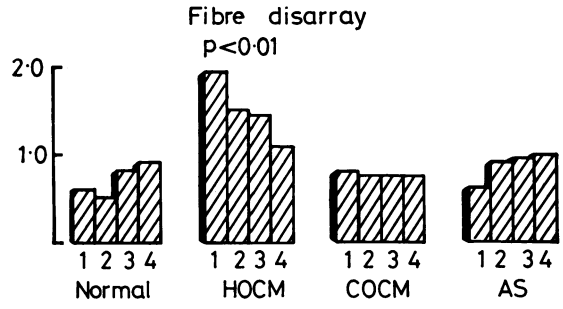

Fig. 5 *Mean of fibre disarray index for section locations 1 to 4 (Fig. 1) for normal hearts, hypertrophic cardiomyopathy (HOCM), congestive cardiomyopathy (COCM), and aortic stenosis (AS). Fibre disarray index was significantly increased in HOCM but was normal in COCM and AS.*

In the transverse axis of the left ventricle, the severity of the fibre disarray index was similar in section locations 1 to 4, and it did not differ significantly in the lower septum, lower lateral left ventricular wall, or right ventricular wall.

Hypertrophic cardiomyopathy (group 2)

In the hearts with hypertrophic cardiomyopathy, the fibre disarray index was significantly increased ($p<0{\cdot}001$). In the left ventricular transverse axis, it varied from 1·3 in the posterior wall to 2·0 in the upper septum (Table 3, Fig. 5). Though the fibre disarray index was consistently greater in the septum than in the free wall, the differences among sections were not statistically significant. The lack of a significant difference in fibre disarray index and, similarly, in the fibrosis index when section locations of the heart were compared does not mean that fibre disarray or fibrosis is homogeneous. It indicates that differences occurring within one heart were not consistently reproduced among other hearts and does not warrant the conclusion that no difference existed. A true difference could possibly exist and yet go undetected because of a relatively small sample size. In addition, the fibre disarray index was comparable in the lower and upper portions of the lateral wall and in the lower and upper parts of the septum; there was no change in severity from the apex to the base of the heart. The fibre disarray index in the right ventricle in hypertrophic cardiomyopathy was normal (Table 3).

Congestive cardiomyopathy (group 3)

The fibre disarray index in hearts with congestive cardiomyopathy varied from 0·7 in the lower lateral left ventricular wall to 1·2 in the lower septum and

1·0 in the right ventricle. There was no statistically significant variation in the severity of fibre disarray among the sections, and no statistically significant difference from the normal group was observed (Table 3, Fig. 5).

Aortic stenosis (group 4)

The fibre disarray index in the hearts with aortic stenosis varied from 0·6 in the upper septum to 1·0 in the posterior left ventricular wall and 0·8 in the right ventricle (Table 3, Fig. 5). These values were very similar to those in congestive cardiomyopathy and were not significantly different from normal in severity or distribution.

WALL THICKNESS

The fibre disarray index in the left ventricle varied independently of wall and septal thickness within the hearts with hypertrophic cardiomyopathy. In hearts with aortic stenosis, wall thickness was significantly increased ($p=0·001$), similar to that in hypertrophic cardiomyopathy ($p<0·001$) (Table 2); in the dilated hearts with congestive cardiomyopathy, in which wall thickness was normal, the fibre disarray index was the same as in aortic stenosis. Thus, these findings indicate that fibre disarray was unrelated to wall thickness, that is, to left ventricular hypertrophy.

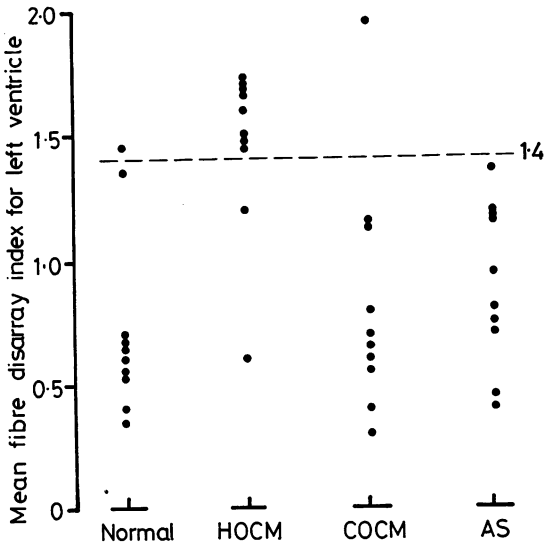

Fig. 6 *Mean fibre disarray index for entire left ventricle in each patient (computed for section locations 1 to 4 and 6 and 7, Fig. 1), in various groups, normals, HOCM, COCM, and AS (abbreviations as before). Reliability of fibre disarray index in separating hearts with HOCM from normals, COCM, and AS is indicated when an arbitrary value of 1·4 is used as a criterion. Two hearts with HOCM are missed and one normal and one COCM heart are incorrectly classified, but no heart with AS is misclassified.*

Table 4 *Microscopical scar index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	Microscopical scar index for each section location (Fig. 1) (Mean and SE)						
		Left ventricle						Right ventricle
		1	2	3	4	6	7	5
Normal	10	0·20 ±0·16	0·07 ±0·07	0·00 —	0·03 ±0·03	0·00 —	0·00 —	0·00 —
HOCM	10	0·17 ±0·11	0·03 ±0·03	0·17 ±0·09	0·23 ±0·14	0·10 ±0·05	0·47 ±0·21	0·03 ±0·03
COCM	10	0·77 ±0·24	0·57 ±0·18	0·40 ±0·22	0·27 ±0·17	0·30 ±0·24	0·17 ±0·10	0·37 ±0·21
AS	10	0·10 ±0·10	0·40 ±0·27	0·23 ±0·17	0·33 ±0·09	0·17 ±0·13	0·63 ±0·32	0·17 ±0·11

* Abbreviations as in Table 1.

The reliability of the fibre disarray index in separating hearts with hypertrophic cardiomyopathy from normals, those with congestive cardiomyopathy, and those with aortic stenosis is indicated in Fig. 6. When 1·4 was used as an arbitrary criterion, two cases of hypertrophic cardiomyopathy were missed and one normal heart and one heart with congestive cardiomyopathy were incorrectly classified, but no case of aortic stenosis was misclassified.

MYOCARDIAL FIBROSIS

In a fashion exactly like that for the fibre disarray index, indices for each of the four types of fibrosis were derived so that hypertrophic and congestive cardiomyopathy and aortic stenosis could be compared with the normal and subsequently with one another.

MICROSCOPICAL SCARS

Microscopical scars were uncommon in normal hearts and were not significantly more common in hypertrophic or congestive cardiomyopathy or aortic stenosis in the right and left ventricles in each group (Table 4, Fig. 7).

INTERSTITIAL FIBROSIS

The interstitial fibrosis index in normal hearts varied little (0·4 to 0·9), and in hypertrophic cardiomyopathy (0·9 to 1·2) it did not differ significantly from normal in the right ventricle or the left ventricle. In congestive cardiomyopathy and aortic stenosis it was significantly ($p=0·002$) increased, 1·3 to 2·0 and 1·4 to 1·8, respectively

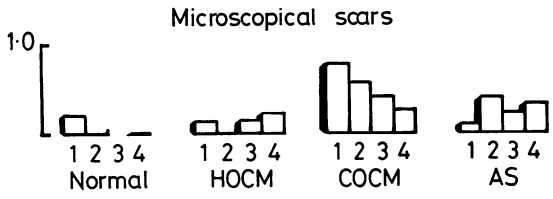

Fig. 7 *Mean of microscopical scar index in normals, HOCM, COCM, and AS (abbreviations as before), showing no significant increase from normal in HOCM, COCM, or AS.*

(Table 5, Fig. 8). Regardless of severity, the differences in interstitial fibrosis index among section locations within each group were not statistically significant.

PERIVASCULAR FIBROSIS

The perivascular fibrosis index in the normal heart was 0·6 to 1·0 in the left ventricle and 0·5 in the right ventricle; in hypertrophic cardiomyopathy it was 0·7 to 1·2 in the left ventricle and 0·6 in the right ventricle, and did not differ significantly from normal. In congestive cardiomyopathy and aortic stenosis, however, perivascular fibrosis indices in the left ventricle were significantly ($p=0·001$) increased, 1·5 to 1·8 and 1·3 to 1·7, respectively (Table 6, Fig. 9) but were not increased in the right ventricle (1·3 and 1·0). Within each group the differences in severity of perivascular fibrosis among section locations (that is, the distribution of perivascular fibrosis) throughout the left ventricle were not statistically significant.

PLEXIFORM FIBROSIS

Plexiform fibrosis occurred in the right ventricle and left ventricle of the hearts of all groups. The plexiform fibrosis index was 0·2 to 0·4 in normals, 0·2 to 0·6 in congestive cardiomyopathy, and 0·2 to 0·6 in aortic stenosis, and the distribution among section locations in the left and right ventricles in all three groups did not vary significantly (Table 7, Fig. 10). In hypertrophic cardiomyopathy, plexiform fibrosis was significantly increased, 0·5 to 1·1 ($p=0·004$), particularly in the septum, where its prevalence was closely associated with fibre disarray (Table 7, Fig. 10).

Table 5 *Interstitial fibrosis index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	Interstitial fibrosis index for each section location (Fig. 1) (Mean and SE)						
		Left ventricle						Right ventricle
		1	2	3	4	6	7	5
Normal	10	0·90 ±0·23	0·47 ±0·15	0·80 ±0·23	0·93 ±0·22	0·43 ±0·14	0·73 ±0·25	0·80 ±0·23
HOCM	10	1·07 ±0·24	1·00 ±0·21	1·13 ±0·13	0·93 ±0·22	1·23 ±0·20	0·87 ±0·25	0·67 ±0·26
COCM	10	2·03 ±0·30	1·67 ±0·29	1·50 ±0·23	1·33 ±0·25	1·50 ±0·27	1·43 ±0·21	1·23 ±0·16
AS	10	1·57 ±0·28	1·47 ±0·29	1·67 ±0·31	1·80 ±0·27	1·37 ±0·35	1·83 ±0·30	1·20 ±0·22

* Abbreviations as in Table 1.

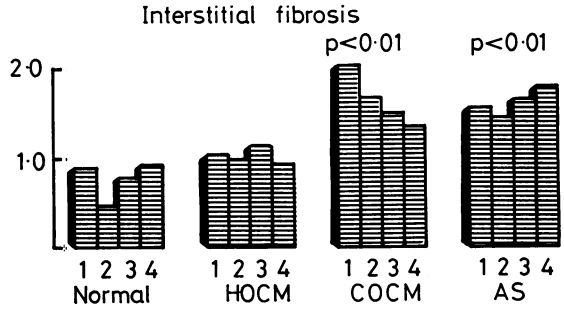

Fig. 8 *Mean of interstitial fibrosis index in normals, HOCM, COCM, and AS (abbreviations as before). Interstitial fibrosis index was normal in HOCM but was significantly increased in both COCM and AS.*

WALL THICKNESS

Wall thicknesses for each section location are shown in Table 2. The indices for all four types of fibrosis varied independently of wall thickness in the left ventricle, both among sections within individual hearts and among hearts within diagnostic groups.

Discussion

Most of the so-called diagnostic features of hypertrophic cardiomyopathy have subsequently been shown to occur also in unrelated anatomical and physiological circumstances; thus, no single clinical or histopathological feature of this disease is pathognomonic. A consistent observation in patients with this disease, however, is the wide spectrum of left ventricular function.[22–24] The purposes of our study were to determine the specificity of fibre disarray in hypertrophic cardiomyopathy, to quantify the severity and distribution of fibre disarray and myocardial fibrosis and their relation to left ventricular hypertrophy in the heart as a whole, and to establish whether an anatomico-pathological basis could be found to account for the variability in left ventricular function.

Myocardial fibre disarray, which had initially

been believed by some investigators to be specific for hypertrophic cardiomyopathy,[1 13 14] has been shown in normal hearts,[18 19] and in a variety of congenital cardiac malformations,[18 20 29 30] in which there appears to be no common pathophysiological mechanism for this change. The non-specific nature of fibre disarray was confirmed in our study, in that it was present in varying degrees in normal hearts and in hearts with congestive cardiomyopathy and aortic stenosis and was similarly distributed among section locations throughout the long and short axes of the left ventricle. Furthermore, the fibre disarray index in the right ventricular wall did not vary significantly among the three disease groups (2 to 4).

In hypertrophic cardiomyopathy, the fibre disarray index was significantly increased in all section locations in the transverse axis of the left ventricle 1 cm below the mitral valve, in the lower lateral left ventricular wall, and in the lower septum. Though the fibre disarray index in hypertrophic cardiomyopathy was numerically slightly higher in the septum than in the free wall, this difference was not significant, in distinct contrast to all the previous qualitative studies.[13 14 30 31] In addition, the fibre disarray index varied independently of wall and septal thickness; this indicated that asymmetric septal hypertrophy is not a prerequisite for fibre disarray. The fibre disarray index in the right ventricle in hypertrophic cardiomyopathy was no different from that in the right ventricle of normal hearts.

Fibre disarray occurred most commonly in the middle third of the septum and free wall (Fig. 2), but this may be explained by the greater facility with which it can be recognised when sections of myocardium are cut parallel to, rather than at right angles to, the myocardial fibre axis. Though fibre disarray *per se* is non-specific, its value as a histological marker was greatly enhanced when both its severity and its distribution within the left ventricle were quantified. When an arbitrary value of 1·4 was selected, it allowed separation of hearts with hypertrophic cardiomyopathy from normal hearts and also from those with aortic stenosis and congestive cardiomyopathy (Fig. 6).

Table 6 *Perivascular fibrosis index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	Perivascular fibrosis index for each section location (Fig. 1) (Mean and SE)						
		Left ventricle						Right ventricle
		1	2	3	4	6	7	5
Normal	10	1·00 ±0·17	0·87 ±0·11	0·93 ±0·13	0·90 ±0·12	0·63 ±0·20	0·80 ±0·11	0·53 ±0·21
HOCM	10	1·17 ±0·18	0·73 ±0·14	1·10 ±0·12	1·23 ±0·17	1·03 ±0·22	1·13 ±0·20	0·60 ±0·16
COCM	10	1·53 ±0·22	1·67 ±0·14	1·77 ±0·28	1·47 ±0·29	1·47 ±0·22	1·67 ±0·12	1·27 ±0·25
AS	10	1·67 ±0·19	1·43 ±0·22	1·63 ±0·22	1·47 ±0·13	1·30 ±0·25	1·57 ±0·19	1·00 ±0·26

* Abbreviations as in Table 1.

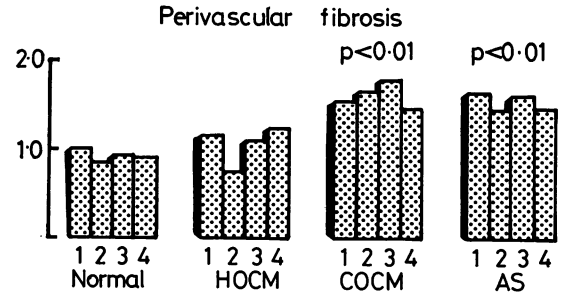

Fig. 9 *Mean of perivascular fibrosis in normals, HOCM, COCM, and AS (abbreviations as before). Perivascular fibrosis index was normal in HOCM but was significantly increased in COCM and AS.*

Of the four types of myocardial fibrosis that were independently assessed, none was specific for hypertrophic cardiomyopathy. In hearts with hypertrophic cardiomyopathy and aortic stenosis, obstruction to left ventricular outflow had resulted in a similar degree of left ventricular hypertrophy, as determined by heart weight and wall thickness. The fact that perivascular and interstitial fibrosis indices were normal in hypertrophic cardiomyopathy but were significantly increased in aortic stenosis suggested that though both groups had left ventricular outflow tract obstruction, different pathophysiological mechanisms were at work.

The perivascular and interstitial fibrosis indices in aortic stenosis and congestive cardiomyopathy were similarly and significantly increased, though wall thickness was normal in congestive cardiomyopathy and significantly increased in aortic stenosis; these findings suggest that these types of fibrosis vary independently of left ventricular hypertrophy. Within all three disease entities (groups 2 to 4), differences in severity of interstitial and perivascular fibrosis among section locations (that is, distribution of these variables) were not statistically significant in the left ventricle. Microscopical scars, which represent replacement of myocardial fibres after cell death, were present in all four groups and the scar index was normal. A further form of myocardial fibrosis, plexiform fibrosis, occurred in all hearts, and it had a similar magnitude and distribution in normal hearts,

congestive cardiomyopathy, and aortic stenosis. It was significantly increased, however, in hypertrophic cardiomyopathy in which it was closely related to fibre disarray.

There is controversy about the cause of fibre disarray in hypertrophic cardiomyopathy. One suggestion has been that the aetiological mechanism is increased wall stress and prolonged isometric contraction,[13 20] for both occur in hypertrophic cardiomyopathy and semilunar valve atresia, in which fibre disarray of a similar severity has been reported.[18] Stress, however, can be mathematically defined as force per unit area, and in the intact heart it equals transmural pressure. Because normal pericardial pressure in man is low (0 to 5 mmHg),[32] peak transmural pressure (that is, peak wall stress) closely approximates peak left ventricular pressure. There are no data to support the suggestion[18] that there is a correlation between left ventricular pressure (wall stress) and fibre disarray in hypertrophic cardiomyopathy.

Although we had no haemodynamic data and therefore could not measure wall stress, we attempted to test indirectly the hypothesis that wall stress resulted in fibre disarray. We selected hearts with left ventricular outflow tract obstruction caused by aortic stenosis with a similar degree of left ventricular hypertrophy (wall thickness and heart weight) to the hearts with hypertrophic cardiomyopathy. The fibre disarray index in hearts with aortic stenosis was significantly less than that in hypertrophic cardiomyopathy, and this indicated that though increased wall stress (that is, increased left ventricular pressure) had "produced" a similar degree of left ventricular hypertrophy, it had not resulted in increased myocardial fibre disarray. Furthermore, in some patients with hypertrophic cardiomyopathy, left ventricular outflow tract gradients are absent at rest and remain small even on pharmacological provocation; consequently, left ventricular pressure and, therefore, wall stress must be close to normal. Fibre disarray has not been reported to be less of a histological marker in patients with small or absent left ventricular outflow pressure gradients than it is in those with large pressure gradients. There is thus little evidence to suggest a relation between fibre disarray and wall stress, and further support for this lack of relation is provided by the existence of fibre disarray in normal hearts and in those with congestive cardiomyopathy.

Table 7 *Plexiform fibrosis index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	Plexiform fibrosis index for each section location (Fig. 1) (Mean and SE)						
		Left ventricle						Right ventricle
		1	2	3	4	6	7	5
Normal	10	0·23 ±0·11	0·23 ±0·11	0·13 ±0·07	0·37 ±0·18	0·17 ±0·13	0·17 ±0·09	0·13 ±0·13
HOCM	10	1·13 ±0·16	0·93 ±0·28	0·70 ±0·10	0·47 ±0·19	0·63 ±0·14	0·53 ±0·15	0·33 ±0·14
COCM	10	0·50 ±0·14	0·60 ±0·27	0·53 ±0·17	0·23 ±0·11	0·27 ±0·14	0·37 ±0·14	0·23 ±0·13
AS	10	0·20 ±0·09	0·53 ±0·17	0·47 ±0·23	0·57 ±0·16	0·43 ±0·19	0·43 ±0·21	0·20 ±0·20

* Abbreviations as in Table 1.

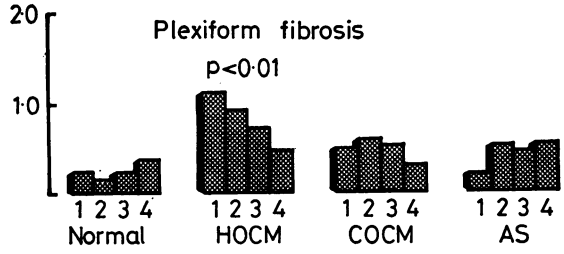

Fig. 10 *Mean of plexiform fibrosis index in normals, HOCM, COCM, and AS (abbreviations as before). Plexiform fibrosis index was significantly increased in HOCM but was normal in COCM and AS.*

An alternative hypothesis has been that contraction-induced linear forces may be important during cardiogenesis in producing normal myocardial fibre architecture and fibre alignment,[33] as they appear to be in the development of other biological tissue such as bone, and that in hypertrophic cardiomyopathy alteration in these directional forces interferes with the parallel alignment of myocardial fibres and results in fibre disarray.[20] This hypothesis, however, does not explain the presence of fibre disarray in normal hearts, nor how it can be induced secondarily in normal animals long after cardiogenesis by the administration of nerve growth factor[34] or by chronic endocardial pacing.[21] For the present, the implication that the fibre disarray in patients with hypertrophic cardiomyopathy who first have cardiovascular symptoms in their sixth or seventh decade has been present since before birth remains conjectural.

A further hypothesis as to the cause of fibre disarray in hypertrophic cardiomyopathy is that it develops because of a primary genetic predisposition,[35] which could explain its presence in a small number of reported cases of this disease at or soon after birth[36] and also its absence in nonfamilial asymmetric septal hypertrophy.[31 37] This hypothesis, however, does not account for the presence

of fibre disarray in semilunar valve atresia[18] and in the conus muscularis of patients with tetralogy of Fallot,[18 30] conditions that are not genetically determined.

We were also unable to explain the presence of fibre disarray in congestive cardiomyopathy but noted that it was significantly more common than in normal hearts throughout the left ventricle, was not significantly more severe in the septum than in the free wall, varied independently of left ventricular hypertrophy, and appeared unrelated to left ventricular wall stress. The fibre disarray index was useful in distinguishing hypertrophic from congestive cardiomyopathy and aortic stenosis when an arbitrary value of $\geqslant 1{\cdot}4$ was chosen (Fig. 6). Interstitial and perivascular forms of fibrosis were normal in hypertrophic cardiomyopathy, but plexiform fibrosis, which was closely associated with myocardial fibre disarray, occurred significantly more often in hearts with hypertrophic cardiomyopathy than in hearts with congestive cardiomyopathy or aortic stenosis. We could not demonstrate a pathological basis in terms of either fibre disarray or fibrosis on which to explain the variability of left ventricular function as shown echocardiographically and angiocardiographically, but this may have been because of the fact that the death of the patients with hypertrophic cardiomyopathy was directly related to left ventricular disease and that the left ventricular free wall and septal myocardium may have reached a similar degree of end-stage cardiomyopathy.

Fibre disarray is thus a non-specific histological feature, as indicated by its presence in normal hearts, aortic stenosis, congestive cardiomyopathy, and a heterogeneous group of congenital cardiac malformations with no common aetiological mechanism. Confusion may have arisen because a solitary causal mechanism has been sought; it probably represents a pathway for diverse pathophysiological processes.

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