Extensive Myocardial Fiber Disarray in Aortic and Pulmonary Atresia
Relevance to Hypertrophic Cardiomyopathy

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SUMMARY Myocardial fiber disarray is a distinctive histopathologic finding seen in asymmetric hypertrophic cardiomyopathy. We studied 14 hearts with aortic atresia and intact interventricular septum, six hearts with pulmonic atresia and intact interventricular septum, eight normal infant hearts matched for age of the study hearts, and one nonadult heart with hypertrophic cardiomyopathy and asymmetric hypertrophy and quantitatively analyzed tissue sections through both ventricles and the septum. Normal hearts had an average overall fiber disarray of 8.7% (range 3.8–17%) of the left ventricle including septum. Hearts with pulmonic atresia had an overall disarray of 70.4% (range 13–97%) of the entire right ventricle, and those with aortic atresia 62.1% (range 26–97%) of the left ventricle. The one infant heart with hypertrophic cardiomyopathy showed 15.5% disorder of the left ventricular free wall, 75% disorder of the septum and 47% overall myocardial fiber disarray. Thus, while quantitative criterion distinguished normal from abnormal hearts, they did not distinguish among the various pathologic states. Although extensive myocardial fiber disarray is not exclusive to, or pathognomonic of, hypertrophic cardiomyopathy, it is a useful finding taken in the context of the overall disease. The sensitivity and specificity of this isolated morphologic observation as an indication of hypertrophic cardiomyopathy may be misleading.

Myocardial fiber disarray was recognized as a striking and characteristic morphologic feature of asymmetric hypertrophic cardiomyopathy when it was originally described by Teare. Later reports of hearts with hypertrophic cardiomyopathy associated with asymmetric septal hypertrophy also described this striking histologic finding, and others have stressed the specificity and, in some cases, pathognomonic quality of the two morphologic features of asymmetric septal hypertrophy and myocardial fiber disarray to the condition. Myocardial fiber disarray is not unique to hypertrophic cardiomyopathy; it can be found, to some degree, in normal hearts and more extensively in hearts with conditions such as pulmonary atresia, aortic atresia and in the infundibular portion of some hearts with tetralogy of Fallot. As the observation of myocardial fiber disarray, per se, cannot distinguish these various cardiac states, quantitative analysis of myocardial fiber disarray was undertaken to distinguish more clearly the fiber disarray of hypertrophic cardiomyopathy from that in other cardiac states.

Maron et al. applied a quantitative method specifically to two congenital heart lesions that were associated with myocardial fiber disarray as extensive, qualitatively, as that seen in hypertrophic cardiomyopathy. They concluded that myocardial fiber disarray was, on the average, 10 times more extensive in hypertrophic cardiomyopathy, and that the histologic finding of extensive myocardial fiber disarray was highly sensitive and specific for hypertrophic cardiomyopathy and was a characteristic feature linking all entities within the spectrum of hypertrophic cardiomyopathy.

This latter finding differs substantially from findings of others, which qualitatively demonstrated myocardial fiber disarray as extensive in some atretic ventricles undergoing isometric contraction as that observed in hypertrophic cardiomyopathy with asymmetric hypertrophy. Therefore, the present quantitative analysis was undertaken.

Materials and Methods

Patients

Patients autopsied at The Johns Hopkins Hospital were selected if they had aortic valve atresia with intact ventricular septum or pulmonic valve atresia with intact ventricular septum, and the gross specimens were available for study. Only hearts in which at least one complete transverse section through the ventricles could be obtained were studied. Fourteen infants (three females and 11 males) with aortic atresia and intact ventricular septum, newborn to 9 months of age, and six patients with pulmonic atresia (one female and five males), intact ventricular septum and small right ventricles, newborn to 9 years of age, were identified. For comparison, eight normal infant hearts (three females and five males), matched for age, and the one infant heart (male, age 5 weeks) with hypertrophic cardiomyopathy and asymmetric hypertrophy autopsied at this institution were studied.

Morphologic Study

Gross specimens were examined and tissue sections through both ventricles and septum (perpendicular to the long axis of the left ventricle) were taken. These sections were embedded in paraffin, sectioned at 5-mm intervals and stained with hematoxylin-eosin. The

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stained sections were photographed with an enlargement of eight to 15 times the histologic section and the portions of interest (ventricular septum, left ventricle, or atretic right ventricle in the cases of pulmonic atresia) were photographically enlarged to an average of 150 times the original section. By simultaneously looking at the enlarged print and viewing the original slide with a light microscope, the disorganized areas of tissue were outlined directly on the print with a wax pencil. The histologic slide had to be examined because of the distortion of focus resulting from enlargement of the negative. Tracing paper was then placed over the print, the outlined areas of disorganization were traced, and the areas of the septum, ventricles, disorganized cells and normally arranged cells were calculated using a Hewlett Packard digitizing computer. The percentage of disorganization of each septum and ventricle was then computed from these figures.

Myocardial fiber disarray of normal hearts, known to be minimal and present almost exclusively in the anterior and posterior portions of interventricular septum, was first determined. Rather than excluding areas that were normally arranged in a nonlongitudinal fashion relative to the transverse section, the normal hearts were used as a guide for determining abnormally organized muscle fibers. We used a method in which no areas of myocardium were excluded to limit observer bias, because we could not “blind” the observer from knowledge of the cardiac lesion being studied. The rationale of restricting the study to infant and children hearts was, in part, to allow for a quantitative determination of myocardial fiber arrangement in a complete transverse section through both ventricles rather than in random sections of free wall or septum.

Definition of Myocardial Fiber Disarray
The normal organization of myocardial fibers in a transverse section through the ventricles (a section perpendicular to the long axis of the heart) is shown in figure 1A. The fibers have been sectioned along their long axis and are arranged in an orderly, parallel array around the ventricular cavity. Fibers of the trabeculae carneae, which constitute the inner third of the ventricular wall, course off at an angle from the middle third of the ventricular wall in a feather-like fashion, but retain a parallel relationship to one another. Figure 1B shows this normal pattern of myocardial fiber organization at higher magnification.

Myocardial fiber disarray is ordinarily defined as the presence of one of the following patterns of organization: fibers branching at sharp angles to one another
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FIGURE 2. (A) Section of left ventricle from a heart with aortic atresia (AA). Portions of myocardium from this heart are shown at higher magnification in B and C and demonstrate the marked myocardial fiber disarray. Hematoxylin-eosin stain; original magnification (A) × 6.4; (B and C) × 65.

(figs. 2B and 3B); groups of fibers cut longitudinally interspersed with fibers cut transversely (fig. 3A); or fibers forming concentric whorls (figs. 2B, 4 and 5B). These patterns of disarray may be found alone or in combination within a given heart (fig. 3B).

Results

Normal Hearts

The bulk of ventricular myocardium had an orderly parallel arrangement of myocardial cells with acute branching at sites of penetrations of the vascular tree and surrounding intramural vessels (fig. 1A). The trabeculae carnae, constituting the inner third of the ventricular wall, course off in a fanning-out appearance, giving a less orderly pattern than the compact portion of ventricular wall. In all instances, a small triangular patch of interlacing muscle cells was present in the anterior and posterior portions of interventricular septum. The areas of “disorganization” constituted 3.8–17% (mean 8.7%) of the entire ventricle, and an average of 17% (range 11.5–29%) of the interventricular septum in transverse section.

Aortic Atresia with Intact Ventricular Septum

Examination of hearts with aortic atresia and intact ventricular septum showed extensive myocardial fiber disorganization of both left ventricular free wall and interventricular septum. The left ventricular cavity was small and the walls were hypertrophied. Instead of the orderly parallel arrangement of myocardial cells seen in the normal left ventricle, the cells are arranged in concentric whorls, or are aligned perpendicularly or obliquely to one another (figs. 2 and 4).

The average amount of disorganization found in the

FIGURE 3. The interventricular septum of a normal heart (A) compared with that of a heart with pulmonic atresia (B). The junction of the right and left ventricle in the interventricular septum shown in A has a patch of disorganization (arrow), but the disarray shown in B is strikingly more extensive. Hematoxylin-eosin stain; original magnification (A) × 13.8; (B) × 13.2.
left ventricular free wall was 58.2% (range 2.9–100%), while disorganization of the interventricular septum was 67.4% (range 16.9–94.3%). The total percent of left ventricular disorganization, including the septum, averaged 62%.

**Pulmonary Atresia With Intact Ventricular Septum**

Hearts with pulmonary atresia and intact ventricular septum (figs. 3B and 6) had a pattern of myocardial fiber disarray similar to that in hearts with aortic atresia. The right ventricular cavities were small and almost obliterated and the right ventricular walls hypertrophied. An average of 68.5% myofiber disarray in the right ventricle free wall (range 17.9–100%), 72.8% disorganization in the interventricular septum (range 3.3–97.3%) and 70.4% overall disorganization were present.

**Hypertrophic Cardiomyopathy With Asymmetry**

Only one infant heart with asymmetric hypertrophic cardiomyopathy was available for study, but was included as a reference for comparison with the atretic and normal ventricles. The one heart with hypertrophic cardiomyopathy (figs. 5A and 7B) had a pattern of

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**FIGURE 4.** Section of left ventricle (LV) from a heart with aortic atresia and intact ventricular septum (sept). Note extensive myocardial fiber disarray of both septum and left ventricular free wall. RV = right ventricle. Hematoxylin-eosin stain; original magnification × 10.8.

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**FIGURE 5.** Myocardial fiber disarray in a heart with hypertrophic cardiomyopathy (A) has a pattern indistinguishable from that in a heart with aortic atresia (B). Hematoxylin-eosin stain; magnification (A and B) × 90.
cellular disarray almost indistinguishable from that in hearts with valvular atresia (fig. 5B). The hypertrophic heart had an average of 15.5% myocardial disorganization of the left ventricle free wall, 75.9% disorganization of the interventricular septum, and an overall myocardial fiber disarray of 47.8%.

**Discussion**

In 1958, Teare et al. described a "new" disease characterized by asymmetric hypertrophy and marked myocardial fiber disarray and associated clinically with sudden death. Subsequently, patients studied clinically with documented asymmetric septal hypertrophy who came to autopsy were found to have this bizarre cardiac pathology. In part because asymmetric septal hypertrophy and myocardial fiber disarray were so unusual, there was much interest in these abnormalities as being pathognomonic, peculiar, sensitive and specific for hypertrophic disease. Maron et al. described myocardial fiber disarray as a morphologic manifestation of the genetically transmitted myocardial disorder, and evidence for this hypothesis was also presented in a study devoted to determining the sensitivity and specificity of myocardial fiber disarray for hypertrophic disease. This study quantitatively analyzed myocardial fiber disarray in a selected section of the interventricular septum, omitting examination of the remainder of the ventricle and excluding portions of the septum. Such a method might allow bias, for myocardial fiber disarray may be a patchy process and evaluation of a single section may grossly under- or overestimate the true extent of the process. With qualitative and quantitative estimations of the amount of myocardial fiber disarray, Maron and Roberts calculated 93% specificity and 90% sensitivity for this isolated morphologic finding as an indicator of the presence of hypertrophic cardiomyopathy. Using this method, they also identified a quantitative difference between hearts with hypertrophic cardiomyopathy and those with atresia, a finding different from that of another study that showed striking similarities of histopathology among these conditions.

Using a quantitative approach similar to that of Maron and Roberts, but without excluding any portions of the ventricle of interest, we have showed, in contrast to Maron et al., that quantitatively extensive...
disorganization of the entire atretic ventricle occurs in hearts with pulmonic and aortic atresia with intact interventricular septum. Our quantitative approach is similar to that of Maron et al. in that both are performed by demarcating areas of disorganization on enlarged photomicrographs, followed by planimetry of these areas to determine a percent figure for this histologic finding. However, the two methods are different in several important ways: First, Maron’s method requires exclusion of substantial portions of the section of myocardium studied, including the junctions of the interventricular septum with right and left ventricles, points of convergence of major muscle bundles and areas adjacent to blood vessels. Because we cannot analyze the histologic sections of atretic ventricles or hypertrophic cardiomyopathy blindly, a method with so many exclusions may pose considerable risk of unintentional observer bias. We chose a method that excluded no areas of myocardium from analysis, with the amount of disarray found in our normal controls serving as a reference value. Second, in our study, which focused on the atretic ventricle, we analyzed myocardial cell disarray for the entire ventricle of interest, rather than limiting the analysis to the interventricular septum. We did this because it is difficult to precisely define the limits of the septum for an atretic ventricle when the ventricular cavity is virtually obliterated. Quantitative data may vary substantially, depending on which radii are chosen to demarcate the limits of the interventricular septum (fig. 8). This problem is eliminated by studying the entire ventricle of interest and including total as well as an area defined as septum. Also, in the study of Bulkley et al., the hypothesis explored was that abnormal stress imposed by isometric contraction could cause myocardial disarray if present early enough in life and long enough. In this human model of isometric contraction, i.e., atresia with intact ventricular septum, the entire atretic ventricle is subjected to abnormal stress, not just the septum; thus, the entire ventricle must be analyzed. Indeed, qualitatively myocardial fiber disarray of the entire atretic ventricle is as extensive as or more extensive than that seen in the septum of idiopathic hypertrophic subaortic stenosis was described. That qualitative observation is in the present study, quantified by a method that is reproducible as well as similar to that of Maron et al.

In this quantitative study (table 1), the hearts with aortic atresia showed myocardial fiber disarray that involved 26–97% of the entire left ventricle, those with pulmonic atresia had overall disarray of 13–97% of right ventricle, and normal hearts had disarray that involved 3.8–17% of left ventricle. In the infant heart with hypertrophic cardiomyopathy, the overall disarray was 48%, with 75% of the septum disorganized. Thus, considering the entire ventricle of interest, the hearts with atresia had as much as or more disorganization than those with hypertrophic cardiomyopathy in this study or in those described by others. Even the untrained observer should be able to see the extensive amount of disarray present in some of these atretic hearts (figs. 2, 4 and 6), compared not only with normal (fig. 1), but also with the hypertrophic heart (fig. 7B). Even without precise quantitation of the photomicrographs, it is apparent from studying these transverse sections that the overall pattern of fiber orientation compared with normal hearts (fig. 1) is markedly disorganized and that the disorganization involves at least one half of the section. Thus, myocardial fiber disarray, when present and especially when present to a marked degree, is most useful in distinguishing normal from abnormal, but as an isolated morphologic finding, does not distinguish specific congenital lesions from hypertrophic cardiomyopathy.

We do not know why some atretic hearts have more disarray than others. A similar heterogeneity has been reported for idiopathic hypertrophic subaortic stenosis. Maron et al. reported a range of 0–94% in 54 interventricular septums. Again, the structural similarities between these small atretic ventricles of infants and the large hearts with asymmetric hypertrophy leads one to question whether a given error in development may be characteristic of both conditions. A common functional derangement — isometric contraction with cavity obliteration — has been suggested. Other factors could be a common genetic, metabolic, neurogenic or

**Figure 8.** Schematic representation of a heart with aortic atresia and cavity obliteration (A) contrasted with a normal heart (B) illustrates the problems of septal delineation and the potential quantitative variation in septal area.

<table>
<thead>
<tr>
<th>Normal (n = 8)</th>
<th>Free wall (%)</th>
<th>Interventricular septum (%)</th>
<th>Total ventricle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.11 (0-9.1)</td>
<td>17 (11-29)</td>
<td>8.7 (3.8-17)</td>
</tr>
<tr>
<td>Pulmonary atresia (n = 6)</td>
<td>68.5 (17-100)</td>
<td>72.8 (3-97)</td>
<td>70.4 (13-97)</td>
</tr>
<tr>
<td>Aortic atresia (n = 15)</td>
<td>58.2 (3-100)</td>
<td>67.4 (16-94)</td>
<td>62.1 (26-97)</td>
</tr>
<tr>
<td>IHSS (one case)</td>
<td>15.5</td>
<td>75.9</td>
<td>47.8</td>
</tr>
</tbody>
</table>

*Left ventricular free wall for normal hearts and those with aortic atresia and IHSS; right ventricular free wall for hearts with pulmonic atresia.

Abbreviation: IHSS = idiopathic hypertrophic subaortic stenosis.

**Table 1.** Myocardial Fiber Disarray of Left Ventricle

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receptor derangement leading to disorganization in myocyte arrangement very early in development.10

Morphology Out of Morphologic Context: Sensitivity and Specificity

There is no question that myocardial fiber disarray, particularly when extensive, is an important and characteristic morphologic abnormality of hearts with hypertrophic cardiomyopathy. Moreover, this finding may well provide information about the pathophysiology of the underlying conditions, particularly when one looks at the rare and diverse states in which such disarray is also present. However, one must question whether myocardial fiber disarray, as an isolated morphologic observation, is sensitive and specific for hypertrophic cardiomyopathy. Such a statement implies that the presence of this morphologic abnormality probably means the disease at hand (i.e., hypertrophic cardiomyopathy), much as the presence of poorly differentiated anaplastic cells from a bronchial washing means cancer. The cell pattern of disorganized myocardial cells is not like anaplastic cells in bronchial washings, since the former can clearly and unequivocally be found in areas of the normal heart and in a variety of conditions that are not hypertrophic cardiomyopathy. Because of this clear overlap with the normal hearts and with other disorders, cellular disarray per se probably does not reflect a specific genetic disorganization peculiar to hypertrophic cardiomyopathy. How do we interpret the data that show myocardial fiber disarray of a given amount is both highly specific and highly sensitive for hypertrophic disease? We should critically examine what it means for this morphologic feature to be specific and sensitive for a given disease. To say that markedly increased myocardial fiber disarray as an isolated finding is sensitive and specific for hypertrophic cardiomyopathy indeed tells one as much about the disease as does the observation that markedly increased abdominal girth is sensitive and specific for pregnancy. Both are morphologic observations out of context; both fix on one structural attribute of a given condition. In a strict statistical sense, both morphologic observations can be shown to be both specific and sensitive for a given condition.

Predictivity reflects the extent to which an abnormal finding indicates disease, and is essential in determining the importance and relevance of a test or observation to the given population in which it is applied. Although myocardial fiber disarray is highly specific and sensitive, it is not nearly as predictive in an unselected population. If one is at a center in which there are many patients with asymmetric hypertrophy, and in which perhaps 60 patients are studied in a mix with 200 normal patients, myocardial fiber disarray would be predictive of hypertrophic disease. In the general hospital autopsy population, however, far fewer of patients with hypertrophic disease are seen, perhaps three per year among 400 or so autopsies. Thus, if even 7% of the 400 without hypertrophic disease have marked myocardial fiber disarray, as shown by others,5,6 most hearts with this histologic abnormality at autopsy would, in fact, not have the disease. Thus, the predictivity of the isolated, out-of-context observation is less than 10%. This calculation shows that the predictive value of a clinical test is related to the incidence of the disease in the population. If the incidence is low in the population to which the test is being applied, the chance that a positive test will be associated with true disease is small.

Morphology in Context

Extensive myocardial fiber disarray is present in hypertrophic disease, but it may also be seen in greater than normal amounts in atretic hearts, in the infundibulum of hearts with tetralogy of Fallot and in the border areas of a myocardial infarction scar.12 The myocardial fibers of embryonal chick hearts develop first in a random alignment and only become organized with progression of cardiogenesis.13 The stimulus for the highly organized alignment of myocardial fibers seen at the completion of cardiogenesis is unknown. Salamander hearts beating in tissue culture lose their orderly myofibril arrangement over time so that marked myocardial fiber disarray is seen after 3 months in tissue culture.14 The finding of myocardial fiber disarray per se in such differing clinical and pathologic contexts suggests not only that this finding is not predictive of hypertrophic cardiomyopathy, but also that it may relate to other abnormalities that may be either structural or functional.

In its proper clinical and pathologic context, however, the observation is important. In the proper pathologic setting — in a human heart without valve disease or congenital abnormality, associated with asymmetric hypertrophy and a small left ventricular cavity — marked myocardial fiber disarray is a useful observation that supports, but does not confirm, the diagnosis of asymmetric hypertrophic cardiomyopathy.

Acknowledgment

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Reference

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Clinical and Echocardiographic Features of Pulmonary Valve Endocarditis

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SUMMARY We studied the clinical and echocardiographic features of eight patients with infective pulmonary valve endocarditis. In two patients, the vegetation was limited to the pulmonary valve; in the six other patients, infective lesions were also present on the mitral or aortic valves. None of the patients were addicted to narcotics. Seven of the eight patients had underlying congenital heart disease. In six patients the organism responsible for the infective endocarditis was Streptococcus viridans.

Two-dimensional echocardiography performed using a wide-angle sector scanner was more useful than M-mode echocardiography for evaluating patients with pulmonary valve endocarditis.

THE INDICENCE of tricuspid valve infective endocarditis has increased markedly, particularly in patients with a history of i.v. drug abuse. Several reports have reviewed the usefulness of two-dimensional echocardiography in detecting abnormal masses associated with tricuspid valve endocarditis. However, few reports have dealt with the echocardiographic and clinical features of pulmonary valve endocarditis. We therefore reviewed the clinical spectrum and echocardiographic features in eight patients with pulmonary valve endocarditis.

Methods

During 5 years, we studied eight consecutive patients on whom morphologic documentation was available at the Heart Institute of Japan. All patients were thought to have infective endocarditis because of fever, positive blood cultures, pulmonary infiltration on chest roentgenograms or murmurs of pulmonary regurgitation. There were six men and two women, ages 18–56 years (average 34 years).

Echocardiograms were recorded within 24 hours of admission to our hospital, and the M-mode examination preceded the two-dimensional study. All patients also underwent repeat echocardiographic examinations every 2 or 3 weeks during medical treatment. Echocardiographic studies were performed with the patient in the left lateral decubitus position. The M-mode echocardiograms were obtained with an Aloka SSD 110 or Irex System 11 ultrasonoscope and a 2.25-MHz transducer focused at 7.5 cm. The transducer was placed in the third or fourth intercostal space just to the left of the sternum. Two-dimensional echocardiograms were performed with a Toshiba-SSH 10A phased-array scanner. Standard techniques were used to perform the examination, and two-dimensional echocardiograms were recorded on videotape.

The echocardiographic diagnosis of vegetation was based on the presence of shaggy echoes or localized extra echoes adherent to the valve not preventing its motion on the M-mode echocardiogram, and a mobile mass that was attached to or appeared to replace normal valve tissue on the two-dimensional echocardiogram.

Surgical or pathologic confirmation was available in all eight patients. Five patients underwent successful valve replacement (four aortic and one mitral) or repair of an intracardiac shunt. One patient died during the follow-up period.

Results

The clinical, pathologic and echocardiographic observations on these eight patients are summarized in Table 1.
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