Quantitative Analysis of Cardiac Muscle Cell Disorganization in the Ventricular Septum

Comparison of Fetuses and Infants with and Without Congenital Heart Disease and Patients with Hypertrophic Cardiomyopathy

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SUMMARY The presence of numerous abnormally arranged cardiac muscle cells in the ventricular septum has been considered a characteristic anatomic feature of hypertrophic cardiomyopathy. However, it has been suggested that the ventricular septum of infants with certain congenital cardiac diseases (such as aortic or pulmonic valve atresia) contains disorganized cardiac muscle cells similar to those in patients with hypertrophic cardiomyopathy. To test the validity of this concept and the true specificity and sensitivity of septal disorganization for hypertrophic cardiomyopathy, sections of ventricular septum were obtained at necropsy from 276 patients and the extent of ventricular septal disorganization was determined quantitatively. Disorganization was most marked in infants, children and adults with hypertrophic cardiomyopathy (i.e., present in 95% of 60 patients); the mean area of septum disorganized was 31 ± 3%. Although disorganized cells were present in 64% of 33 infants with aortic or pulmonic valve atresia, these cells occupied extremely small areas of ventricular septum (mean area of septum disorganized 2.8 ± 0.7%; p < 0.001). Furthermore, the minimal septal disorganization present in aortic or pulmonic valve atresia was similar to that found in 91 infants with other congenital heart malformations and in 92 normal fetuses or infants (mean area of septum disorganized was 1.4 ± 0.6 and 0.3 ± 0.1%, respectively). Hence, extensive ventricular septal disorganization is highly sensitive and specific finding for hypertrophic cardiomyopathy, although small areas of disorganization may occur in infants with other heart diseases, including aortic or pulmonic valve atresia.

IN THE INITIAL REPORT of hypertrophic cardiomyopathy, Teare\(^1\) described a bizarre arrangement of cardiac muscle cells in the asymmetrically hypertrophied ventricular septum. Subsequently, other investigators made similar observations regarding the histologic appearance of ventricular septal myocardium in this disease.\(^2\)\(^-\)\(^9\) A recent report, based on a qualitative histologic analysis, emphasized that the ventricular septum of infants with aortic or pulmonic valve atresia contains disorganized cardiac muscle cells similar to those in patients with hypertrophic cardiomyopathy.\(^10\) Recent experience with a quantitative method for assessing the extent of cellular disorganization in the ventricular septum has shown that it is not the presence or absence but rather the extent of septal disorganization that distinguishes patients with hypertrophic cardiomyopathy from those with other heart diseases histologically.\(^11\) Hence, we undertook the present study to determine the relative extent of cardiac muscle cell disorganization in the ventricular septum of infants with congenital heart disease (including those with aortic or pulmonic valve atresia) compared with that of patients with hypertrophic cardiomyopathy.

Selection of Case Material

We reviewed the cardiovascular registries of the Pathology Branch, National Heart, Lung, and Blood Institute, United Hospitals-Miller Division, and the Children's Hospital Medical Center and selected 276 hearts for study. The following subgroups of hearts were included:

1) 23 infants with aortic valve atresia, hypoplastic left ventricle and intact ventricular septum (The mitral valve was hypoplastic in 20 patients and atretic in the other three.);\(^12\)

2) 10 infants with pulmonic valve atresia, hypoplastic right ventricle, intact ventricular septum and nonatretic tricuspid valve. Because the ventricular wall thicknesses and histologic findings in patients with aortic or pulmonic valve atresia (with or without atretic mitral valve) did not differ appreciably, these two groups of patients were combined for convenience in data analysis;

3) 91 infants with a variety of congenital heart malformations other than aortic or pulmonic valve atresia, in which the ventricular cavities were not hypoplastic;

4) 29 fetuses (10-22 weeks gestation), without evidence of structural cardiac disease, obtained from therapeutic abortions.\(^13\)
5) 14 live-born premature infants of 23–35 weeks gestation who died in the first 4 days of life due to septicemia or intracranial hemorrhage, and five stillborn infants, none of whom had evidence of structural cardiac disease;

6) 44 live-born term infants, without evidence of structural cardiac disease, who died from 1 day to 20 months of age due to trauma, septicemia, diaphragmatic hernia, or complications of delivery. For the purposes of data analysis, the fetuses, live-born premature infants, stillborns and live-born term infants were combined as a group of normal fetuses and infants;

7) 60 patients with hypertrophic cardiomyopathy, including six infants (stillborn to 11 months of age), 10 children (11–17 years of age), and 44 adults (18–70 years of age).

In the infants with congenital heart disease, death resulted from complications of cardiac catheterization, operative or postoperative complications, congestive heart failure, or sudden death, presumably due to ventricular arrhythmia (in nonoperated patients). Patients with hypertrophic cardiomyopathy, infants with congenital heart disease, and normal fetuses and infants are compared with regard to clinical and morphologic parameters in table 1.

### Materials and Methods

#### Measurement of Ventricular Wall Thicknesses

Measurements of ventricular wall thicknesses were made in two areas: 1) in the ventricular septum, at the point of maximum thickness, usually about one-half the distance between the base of the aortic valve and the apex of the left ventricle; and 2) in the posterior left ventricular wall, behind the midpoint of the posterior mitral leaflet, at a level corresponding to the tips of the mitral leaflets. These measurements were made perpendicular to the endocardial surface of the ventricular walls (with calipers in infants and with a light microscope and calibrated micrometer eyepiece in fetuses). Trabeculations, papillary muscles, crista supraventricularis and mitral and tricuspid valve structures were not included in the measurements of ventricular wall thickness.

#### Tissue Preparation

In each patient in this study, tissue blocks were taken from the full thickness of ventricular septum, at the point of maximal thickness, about one-half the distance between the base of the aortic valve and the apex of the left ventricle, and in a plane perpendicular to the long axis of the left ventricle (i.e., the transverse

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**Table 1. Clinical and Morphologic Data in Four Subgroups of Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertrophic cardiomyopathy (n = 60)</th>
<th>Aortic or pulmonic atresia** (n = 33)</th>
<th>Other congenital heart diseases$ (n = 91)</th>
<th>Normal fetuses and infants (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>27 years (stillborn–70 years)</td>
<td>3 days (1–60 days)</td>
<td>1 month (1 day–2 years)</td>
<td>Fetuses: 24 weeks gestation (10–35 weeks) Infants: 6 weeks (1 day–20 months)</td>
</tr>
<tr>
<td>Sex (% male:female)</td>
<td>43:57</td>
<td>76:24</td>
<td>57:43</td>
<td>54:46*</td>
</tr>
<tr>
<td>VS thickness (mm)</td>
<td>25 ± 1</td>
<td>5 ± 0.3</td>
<td>6 ± 0.2</td>
<td>Fetuses: 2 ± 0.1 Infants: 5 ± 0.1</td>
</tr>
<tr>
<td>VS/PW</td>
<td>1.7 ± 0.06</td>
<td>1.0 ± 0.04</td>
<td>1.1 ± 0.03</td>
<td>Fetuses: 1.5 ± 0.05 Infants: 1.1 ± 0.03</td>
</tr>
<tr>
<td>VS/PW ≥ 1.3 (%)</td>
<td>90‡</td>
<td>9</td>
<td>25</td>
<td>Fetuses: 69 Infants: 25</td>
</tr>
<tr>
<td>Patients with disorganization (%)</td>
<td>95</td>
<td>64</td>
<td>12</td>
<td>8‡</td>
</tr>
<tr>
<td>Area of VS disorganized (%)</td>
<td>31 ± 3</td>
<td>2.8 ± 0.7</td>
<td>1.4 ± 0.3</td>
<td>0.3 ± 0.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Data included for only 44 live-born term infants.

†Of the seven patients in this subgroup with disorganization, four were fetuses and three were term infants.

‡In each of the 60 patients, the diagnosis of hypertrophic cardiomyopathy was based on the presence of a hypertrophied, nondilated left ventricle (in the absence of a cardiac or systemic disease that itself could produce left ventricular hypertrophy). In 54 (90%) of the 60 patients, asymmetric septal hypertrophy (defined as a septal-free wall thickness ratio of ≥ 1.3) was present at necropsy. In the remaining six patients with hypertrophic cardiomyopathy, concentric ventricular wall thickening (septal-free wall ratio < 1.3) was present at necropsy.

§Congenital heart malformations included the following: complete (− D) transposition of the great vessels (n = 14), coarctation of the aorta (n = 11), truncus arteriosus (n = 11), ventricular septal defect (n = 7), total anomalous pulmonary return (n = 7), valvular aortic stenosis (n = 6), Ebstein's malfunction of the tricuspid valve (n = 6), double outlet right ventricle (n = 5), valvular pulmonary stenosis with intact ventricular septum (n = 5), tetralogy of Fallot (n = 5), tricuspid atresia (n = 5), ventricular septal defect and pulmonary stenosis (n = 4), cor triatriatum (n = 3), congenital mitral stenosis and ventricular septal defect (n = 1), and primary pulmonary hypertension (n = 1).

Includes 29 fetuses, 14 premature infants and five stillborn infants.

**Infants with aortic valve atresia did not differ significantly from those with pulmonic valve atresia with regard to each of the parameters in the table.
plane). In the anteroposterior axis, these sections extended to the point of junction of the ventricular septum with the left and right ventricular free walls. (We have previously shown that transverse plane tissue sections are the most appropriate for identifying cardiac muscle cell disorganization.) In hearts with aortic or pulmonic valve atresia, we defined the ventricular septum as the segment of ventricular myocardium between the endocardium of the hypoplastic ventricular cavity and the endocardium of the dilated ventricular cavity (fig. 1). All tissue specimens were embedded in paraffin, sectioned at a thickness of 6 µ and stained with hematoxylin and eosin.

Definition and Classification of Cardiac Muscle Cell Disorganization

In contrast to normal cellular arrangement, the cardiac muscle cell disorganization observed in the infants, children and adults in this study assumed five different forms, which have been described in detail previously (fig. 4). Type I-A disorganization, the most common form encountered, consisted of areas of myocardium in which adjacent cardiac muscle cells were aligned perpendicularly or obliquely to each other, usually forming tangled masses or “pinwheel” configurations. Although most of these lesions were small, individual foci of type I-A disorganization varied greatly in size (particularly in patients with hypertrophic cardiomyopathy). In Type I-B disorganization, relatively broad bundles of muscle cells were oriented at oblique or perpendicular angles to each other; cells within these bundles were, however, normally arranged. Types I-A and I-B exclusively involved areas of ventricular septum where cardiac muscle cells were cut longitudinally, i.e., appeared to be rectangularly shaped.

Type II-A disorganization consisted of relatively narrow (usually one or two cells wide), longitudinally cut bundles of cells that were interlaced in various directions among larger groups of transversely cut cells (i.e., appeared circular). This type of disorganization gave the myocardium a swirled appearance. Type II-B was similar to type II-A disorganization, except that the narrow, longitudinally cut bundles of cells were more linear. Type II-C consisted of relatively small “islands” of disorganized, longitudinally cut cells within much larger areas of transversely cut cells. The three forms of type II disorganization involved both longitudinally and transversely cut cardiac muscle cells.

Nonparallel arrangements of cardiac muscle cells were not considered to represent disorganization if present in the following areas where cells normally converge at acute angles: 1) at or near the junction of ventricular septum with the left and right ventricular free walls; 2) in trabeculations; 3) in or at the edges of scarred areas; 4) at points of convergence of major muscle bundles; or 5) adjacent to interstitial spaces containing blood vessels.

Quantitation of Cardiac Muscle Cell Arrangement

We used a technique, previously described in detail, to quantitatively assess the extent of cardiac muscle cell disorganization in tissue sections of ventricular septum from the 276 hearts studied. In brief, tissue sections (in which cardiac muscle cell disorganization was judged to be present qualitatively) were photographed and the images enlarged to occupy 30" × 40" positive prints, resulting in an average magnification of about 5000 times the original tissue section. A transparent cellulose overlay was then placed over the print, and the areas of myocardium occupied by disorganized cardiac muscle cells were outlined with a marking pen on the transparent overlay. Although we could often make this assessment exclusively from direct examination of the print, we frequently had to reexamine the original tissue section with a light microscope to localize the disorganized area. We also demarcated areas in which cardiac muscle cells were cut either longitudinally or transversely. Large areas of fibrosis (replacement or interstitial), artifacts of tissue preparation or large interstitial spaces with blood vessels also were outlined and excluded from the analysis. The transparent overlay was then removed from the print, photo-
FIGURE 2. Example of normal cellular arrangement in the ventricular septum of a 3-day-old infant with aortic valve atresia. Adjacent cardiac muscle cells are in a rigidly parallel relation to each other (magnification × 80; hematoxylin and eosin stain).

Graphed and the image reproduced (with substantial reduction) as a 5 × 7-inch positive print. Each area into which the tissue section had been divided was outlined separately with a fine-point marking pen on ordinary tablet paper, and quantitated using a video planimetry system. Two investigators independently analyzed the print enlargements, usually without knowledge of whether the tissue section was from a patient with hypertrophic cardiomyopathy. Often, however, recognition of the patient's disease was unavoidable because a particularly large tissue section strongly suggested hypertrophic cardiomyopathy.

Formulas Used in Quantitative Calculations of Cardiac Muscle Cell Arrangement

The formulas used to calculate the percent area of ventricular septum occupied by disorganized cardiac muscle cells are given below; the area of septum “at risk” for disorganization appears in the denominator of both equations:
% area of type I (I-A + I-B) disorganization = \[ \frac{D_1}{L + D_1} \times 100; \]

% area of type II (II-A + II-B + II-C) disorganization = \[ \frac{D_{II}}{L + T + D_{II}} \times 100; \]

where L = area occupied by longitudinally cut but normally arranged cells, T = area occupied by transversely cut cells (excluding those incorporated into areas of type II disorganization), D_1 = area occupied by type I disorganization, and D_{II} = area occupied by type II disorganization.

We could not combine values for types I and II disorganization in patients who had both types, because this calculation often resulted in a marked underestimation of the overall extent of disorganization in a tissue section. Hence, the percent septal disorganization plotted for each patient was the value for type I or type II disorganization, whichever value was greater. We did not attempt to assess the degree of cel-

**Figure 3.** Several other examples of cardiac muscle cell arrangements that were not considered to constitute true abnormalities. A) and B) Minor deviations in alignment from the rigid parallelism shown in figure 2; magnification × 220. C) Small "fascicle" of transversely cut cells in an area where two muscle bundles converge acutely; magnification × 80. D) A single narrow band of longitudinally cut cells traverses a larger area of transversely cut cells; magnification × 130. All specimens were stained with hematoxylin and eosin.
lular malalignment in a given area of tissue. Rather, septal disorganization was judged only to be present or absent, and its severity was expressed in terms of extent (as discussed above).

Results

Ventricular Wall Thicknesses

Ventricular septal thicknesses and septal-free wall ratios for each of the four subgroups of patients are summarized in Table 1. Disproportionate septal thickening (septal-free wall ratio ≥ 1.34 to 1.7) was significantly more prevalent in patients with hypertrophic cardiomyopathy (48 of 60 patients or 80%) than in any other patient group (p < 0.001), and was least common in the infants with aortic or pulmonic valve atresia (three of 33 patients or 9%; p < 0.001). The septal-free wall ratios in patients with aortic or pulmonic valve atresia (mean 1.0 ± 0.04 mm) (± SEM) were also significantly less than in patients with other congenital heart diseases or in normal term infants (p < 0.01).

Morphologic Appearance of the Ventricular Septum

The architecture of large muscle bundles in the ventricular septum was relatively uniform in the vast majority of patients studied. A narrow bundle of longitudinally cut cardiac muscle cells was usually present in the center of the tissue section extending from the anterior to the posterior limits of the ventricular septum; this band usually comprised one-third (in adult patients) to one-half (in fetuses and infants) of the overall tissue section area (Table 2). Transversely cut cells were present, for the most part, in the areas on either side of the central band (adjacent to the left and right ventricular cavities).

In infants with aortic or pulmonic valve atresia, the ventricular septum was particularly small because of the diminutive size of either the left or right ventricular cavity (Fig. 1). In 19 of the 23 hearts with aortic valve atresia (none of the four with associated mitral valve atresia), the endocardium was diffusely thickened. In 16 of these 19 patients, the endocardial thickening was particularly marked, and the endocardium comprised at least 10% of the overall septal thickness, and more than 40% of septal thickness in three (Fig. 5). In 15 of these 16 patients with aortic valve atresia and markedly thickened endocardium, one or more of the following structural alterations were present at the interface between endocardium and myocardium: cardiac muscle cells with evidence of degeneration (resembling myocytolysis in the eosin-stain), calcific deposits, or foci of disorganized cardiac muscle cells.

A relatively small endocardial fibrous plaque was present on the left ventricular septal surface in sections from 10 patients with hypertrophic cardiomyopathy. These plaques were quite localized in extent compared with those seen in aortic valve atresia.

Quantitative Histologic Findings

Patients with hypertrophic cardiomyopathy and fetuses or infants in the other three subgroups differed markedly with respect to both the occurrence and extent of ventricular septal disorganization (Table 1 and 2). Disorganization was significantly more common in patients with hypertrophic cardiomyopathy (57 of 60, or 95%; p < 0.001) than in any of the other three subgroups of fetuses and/or infants studied. Of the three subgroups, the prevalence of septal disorganization was highest in infants with aortic or pulmonic valve atresia.
atresia (21 of 33, or 64%); overall, only 39 (18%) of the 216 infants with congenital heart disease or normals showed disorganization.

Most importantly, patients with hypertrophic cardiomyopathy and the three subgroups of fetuses and/or infants differed markedly with respect to the extent of ventricular septal disorganization (figs. 6–8). The mean percent area of septum disorganized in patients with hypertrophic cardiomyopathy was 31 ± 3% (range 0–94%); the extent of disorganization in infants with hypertrophic cardiomyopathy did not differ significantly from that in children or adults with this disease. Furthermore, 90% of the patients with hypertrophic cardiomyopathy had disorganization occupying 5% or more of the relevant areas of the tissue section, 56% of the patients had ≥ 25% of the section involved and 25% of the patients had more than 50% involved. In contrast, only 16 (7%) of the 216 infants with congenital heart disease or normals had disorganization involving more than 5% of the relevant areas of the septal tissue section; in nine other fetuses or infants, the area of septum disorganized was < 1% of the tissue section. Only one infant with congenital heart disease (tricuspid atresia) had > 25% of the section involved by disorganization.

The cut point that appeared to best distinguish patients with hypertrophic cardiomyopathy from infants with other diseases, histologically, was septal disorganization involving 5% or more of the relevant parts of the tissue section. Therefore, septal disorganization of ≥ 5% is consistent with the histologic diagnosis of hypertrophic cardiomyopathy, while sep-

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Percent area of ventricular septum occupied by disorganized cardiac muscle cells in 60 patients with hypertrophic cardiomyopathy (six infants are designated by triangles), 33 infants with aortic or pulmonic valve atresia (patients with pulmonic atresia are designated by open circles), 91 infants with other congenital heart diseases associated with normal-sized or dilated ventricular cavities, and 92 normal fetuses or infants. ϖ = mean value.
HYPERTROPHIC CARDIOMYOPATHY

AORTIC VALVE ATRESIA

FIGURE 7. Representative "maps" of ventricular septum from two infants with type I-A disorganization. Both sections were obtained in a plane perpendicular to the long axis of the left ventricle. The septum of a 5-month-old infant with hypertrophic cardiomyopathy is shown above. The septum of a 4-day-old infant with aortic valve atresia and concentric ventricular hypertrophy is shown below (see figure 2 for photomicrograph from the same patient). The striped areas represent normally arranged cardiac muscle cells cut longitudinally; the clear areas adjacent to the left (LV) and right ventricular (RV) cavities contain cells cut transversely. The solid areas represent foci of type I disorganization; the stippled area represents a focus of type II disorganization. In the patient with hypertrophic cardiomyopathy, disorganized cardiac muscle cells occupy about 33% of the relatively small striped area; in contrast, the disorganized areas are very small (both individually and in summation) in the patient with aortic valve atresia, and together represent only 2% of the relevant parts of the tissue section.

tal disorganization of < 5% makes this diagnosis unlikely.

Some overlap in terms of percent septal disorganization was present between the four subgroups of patients studied; however, the mean area of septum disorganized in each of the three groups of fetuses and/or infants was quite small (< 3%), and when the three groups were combined, the mean value was only 1.2 ± 0.3%. In each subgroup of fetuses and/or in-

FIGURE 8. Extent of septal disorganization in 60 patients with hypertrophic cardiomyopathy and 216 control fetuses and infants. Each of the comparisons achieved high statistical significance (p < 0.001).

fants, the extent of disorganization was significantly less than that found in patients with hypertrophic cardiomyopathy (p < 0.001; fig. 6).

At relatively high magnification, the small areas of disorganization present in some infants with aortic or pulmonic valve atresia, as well as in those with other congenital heart malformations or normal hearts (fig. 9A), appeared qualitatively identical to the widespread lesions present in patients with hypertrophic cardiomyopathy. However, at lower magnification such areas of disorganization were barely discernible and obviously constituted only a small part of the tissue section (fig. 9B).

Abnormally arranged cardiac muscle cells were most common in the middle one-third of the ventricular septum (in hearts with and without hypertrophic cardiomyopathy). However, it is in the middle one-third of the septum that longitudinally cut cells are usually present in tissue sections taken perpendicular to the long axis of the left ventricle. Hence, it would be expected that the common type I disorganization, which can only be identified in areas of longitudinally cut cells, would be observed most frequently in the middle one-third of the transverse plane sections obtained in this study.

Type I disorganization (in particular type I-A) was the most common form encountered in patients with hypertrophic cardiomyopathy and in infants with other congenital heart diseases (table 2). In contrast, type II disorganization predominated in the normal fetuses and infants.

In 15 of the infants with congenital heart diseases other than hypertrophic cardiomyopathy, alterations in cardiac muscle cell arrangement were present in the area of ventricular septum adjacent to a markedly
thickened endocardium (≥ 10% of the total septal thickness) (fig. 10). This phenomenon was most common in infants with aortic valve atresia (10 patients), but it also occurred in three patients with normal-sized left ventricular cavities and either aortic valve stenosis or coarctation of the aorta, in one patient with pulmonic valve atresia and small right ventricular cavity, and in one patient with Ebstein's anomaly of the tricuspid valve. The areas of subendocardial disorganization in these patients were relatively small (mean 5 ± 1%) and did not differ significantly in size from areas of disorganization present in other regions of the septum in eight of the patients (mean 3 ± 1%). Alterations in cellular arrangement in the subendocardial region of the septum were of the type II variety in 14 patients and type I in the other patient.

Discussion

The findings of this quantitative morphologic study indicate that while small areas of cardiac muscle cell disorganization may occasionally occur in the ventricular septum of normal fetuses or infants or of infants with a variety of congenital heart diseases, extensive septal disorganization is exceedingly uncommon. For example, while 18% of the 216 patients with normal hearts or with diseases other than hypertrophic cardiomyopathy had some disorganization in the ventricular septum, only 7% of the 216 patients had disorganization occupying more than 5% of the relevant areas of the septal tissue section (our criterion for extensive disorganization).\(^{11}\) Furthermore, the mean area of septum disorganized in these 216 patients was minimal (1.2 ± 0.3%). Indeed, the specificity of extensive septal disorganization in our necropsy population of 216 patients without hypertrophic cardiomyopathy was high (93%). These findings were similar to those of a previous quantitative histologic analysis of ventricular septum in 144 older children and adults with normal hearts or hearts with a variety of congenital or acquired heart defects, in which only 7% of the patients had extensive septal disorganization and the mean area of septum disorganized was 1.5 ± 0.6%.\(^{11}\)

In contrast, 90% of the 60 patients with hypertrophic cardiomyopathy (including infants, children and adults) had disorganization occupying 5% or more of the tissue section, over 50% of the patients had ≥ 25% of the section involved, and about 25% of the patients had more than 50% involved. Of the 60 patients with hypertrophic cardiomyopathy, the mean area of septum disorganized was substantial (31 ± 3%). Indeed, the sensitivity of extensive septal disorganization in our necropsy population of 60 patients with hypertrophic cardiomyopathy was also high (90%).

The quantitative histologic findings in infants with aortic or pulmonic valve atresia showed that cellular disorganization in the ventricular septum of these hearts was relatively common; however, the disorganization generally involved extremely small areas of myocardium, in contrast to the widespread septal

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**FIGURE 9.** Two photomicrographs of the same area of ventricular septal myocardium from a 3-day-old infant with a normal heart. A) An area of type I-B disorganization is shown at relatively high magnification (×350); B) same area of myocardium shown at a much lower magnification (×55). The area of disorganization (outlined by broken line), so impressive at higher magnification, is barely discernible here and obviously constitutes an extremely small part of the overall tissue section. Each specimen was stained with hematoxylin and eosin.
Table 2. Quantitative Histologic Findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertrophic cardiomyopathy</th>
<th>Aortic or pulmonic valve atresia</th>
<th>Other congenital heart diseases</th>
<th>Normal fetuses and infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SEM</td>
<td>n</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>Size of septal tissue section (cm²)</td>
<td>60</td>
<td>4.4 ± 0.4</td>
<td>33</td>
<td>0.4 ± 0.04</td>
</tr>
<tr>
<td>Area of longitudinally cut cells in septum (%)</td>
<td>60</td>
<td>34 ± 2</td>
<td>15*</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>Area of septum disorganized (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I (I-A + I-B)</td>
<td>57</td>
<td>31 ± 3</td>
<td>15</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(II-A + II-B + II-C)</td>
<td>12</td>
<td>8 ± 2</td>
<td>17</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Type I or II†</td>
<td>60</td>
<td>31 ± 3</td>
<td>33</td>
<td>2.8 ± 0.7</td>
</tr>
</tbody>
</table>

* Determined only in patients with cardiac muscle cell disorganization.
† Value for percent area of septum disorganized used for each patient was that of either type I or type II disorganization, whichever was greater.

disorganization usually present in patients with hypertrophic cardiomyopathy. For example, disorganization was trivial (≤ 1% of the tissue section) in one-third of the hearts with aortic or pulmonic valve atresia that had disorganization. Most importantly, the extent of septal disorganization in infants with aortic or pulmonic valve atresia did not differ significantly from that in infants with a variety of other congenital cardiac malformations associated with nonatretic ventricles. Hence, histologically, aortic or pulmonic atresia are no more similar to hypertrophic cardiomyopathy than are other congenital heart malformations.

The ventricular septum of hearts with aortic valve

Figure 10. Areas of ventricular septum directly adjacent to a markedly thickened endocardium (ENDO) in two infants with aortic valve atresia. A) Alteration in cellular arrangement of the Type II-A variety; magnification × 55. B) Small area of type I-A disorganization; magnification × 80. Both were stained with hematoxylin and eosin. Arrows denote disorganized cardiac muscle cells.
Atresia commonly showed alterations in cellular arrangement directly beneath a markedly thickened endocardium (overlying the left septal surface). Nonparallel cellular arrangement at this interface between endocardium and myocardium is probably created by the severely malformed anatomy apparent in this area of the heart and probably should not be considered to be true disorganization. However, even with such alterations in cellular arrangement in the subendoocardial region included in our data analysis as true abnormalities of septal architecture, disorganization was still much more extensive in patients with hypertrophic cardiomyopathy than in infants with aortic valve atresia or other congenital heart diseases. If subendoocardial cellular alterations were excluded from the analysis, the mean area of septum disorganized in patients with aortic or pulmonic valve atresia would be reduced from 2.8 ± 0.7% to 1.3 ± 0.5%.

Therefore, we found no consistent morphologic similarities in the extent of septal disorganization or the prevalence of disproportionate septal thickening between hearts with aortic or pulmonic valve atresia and hearts with hypertrophic cardiomyopathy. These findings differ appreciably from those recently reported in a similar group of infants (in which quantitative analysis of septal disorganization was not undertaken) and do not support the contention that hypertrophic cardiomyopathy and aortic or pulmonic valve atresia have similar morphologic characteristics because of the theoretical possibility that hearts with these diseases each undergo a prolonged period of isometric contraction during ventricular systole. Hence, the findings presented in this report further support our previous hypothesis,7,11 based on both qualitative7,10,11 and quantitative11 histologic analysis, that extensive cardiac muscle cell disorganization in ventricular septal myocardium is a highly sensitive and specific marker for hypertrophic cardiomyopathy, even though the presence per se of septal disorganization is not pathognomonic of hypertrophic cardiomyopathy.

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References


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