Structural Abnormalities of Great Arterial Walls in Congenital Heart Disease

Light and Electron Microscopic Analyses

Koichiro Niwa, MD; Joseph K. Perloff, MD; Sunita M. Bhuta, MD; Hillel Laks, MD; Davis C. Drinkwater, MD; John S. Child, MD; Pamela D. Miner, NP

Background—Great arteries in congenital heart disease (CHD) may dilate, become aneurysmal, or rupture. Little is known about medial abnormalities in these arterial walls. Accordingly, we studied 18 types of CHD in patients from neonates to older adults.

Methods and Results—Intraoperative biopsies from ascending aorta, paracoarctation aorta, truncus arteriosus, and pulmonary trunk in 86 patients were supplemented by 16 necropsy specimens. The 102 patients were 3 weeks to 81 years old (average, 32.6 years). Biopsies were examined by light (LM) and electron (EM) microscopy; necropsy specimens by LM. Positive aortic controls were from 15 Marfan patients. Negative aortic controls were from 11 coronary artery disease patients and 1 transplant donor. Nine biopsies from acquired trileaflet aortic stenosis were compared with biopsies from bicuspid aortic stenosis. Negative pulmonary trunk controls were from 7 coronary artery disease patients. A grading system consisted of negative controls and grades 1, 2, and 3 (positive controls) based on LM and EM examination of medial constituents.

Conclusions—Medial abnormalities in ascending aorta, paracoarctation aorta, truncus arteriosus, and pulmonary trunk were prevalent in patients with a variety of forms of CHD encompassing a wide age range. Aortic abnormalities may predispose to dilatation, aneurysm, and rupture. Pulmonary trunk abnormalities may predispose to dilatation and aneurysm; hypertensive aneurysms may rupture. Pivotal questions are whether these abnormalities are inherent or acquired, whether CHD plays a causal or facilitating role, and whether genetic determinants are operative. (Circulation. 2001;103:393-400.)

Key Words: aorta ■ lung ■ arteries ■ heart defects, congenital

The ascending aorta and pulmonary trunk in congenital heart disease (CHD) may dilate out of proportion to hemodynamic or morphogenetic expectations, may become aneurysmal, and may rupture.1-4 Comparatively little attention has been paid, however, to the prevalence, range, and degree of abnormalities of great arterial media.5-11 Using Marfan syndrome or annuloaortic ectasia as prototypical extremes,12-14 we undertook a light microscopic (LM) and electron microscopic (EM) study of surgically secured biopsies, supplemented by necropsy specimens, in patients with a wide variety of CHDs from neonates to older adults.

Methods

Between 1995 and 1999, full-thickness transmural intraoperative biopsies were obtained from ascending aorta or truncus arteriosus several centimeters distal to the sinotubular junction, from proximal and distal paracoarctation aorta, and from the midportion of the pulmonary trunk in 86 patients with CHD, and from 1 right pulmonary arterial aneurysm in an extirpated heart/lung specimen (Tables 1 and 2). Patients were initially selected because great arterial dilatation exceeded expectations. Subsequently included were ascending aortic biopsies from 8 neonates with complete transposition of nondilated great arteries and biopsies from 5 infants with truncus arteriosus. Also included were 16 necropsy specimens from adults with truncus arteriosus, or ascending aortic or pulmonary trunk dilatation, aneurysm, or rupture (Tables 2 and 3). The 103 patients (from whom 86 biopsies, 16 necropsies, and 1 extirpated specimen were taken) were 3 weeks to 81 years old (average, 32.6 years) and showed 18 varieties of CHD (Tables 1 to 3). Biopsies from proximal and distal paracoarctation aorta were counted as 1 sample. When coarctation and bicuspid aortic valve coexisted, biopsies were from the paracoarctation aorta. When a bicuspid aortic valve existed without coarctation, biopsies were from the ascending aorta. Sources of aortic biopsy and necropsy specimens appear in Tables 1 and 3; pulmonary arterial specimens in Table 2; and truncus arteriosus specimens in Table 3. No patient, including those with grade 3 medial abnormalities, had a connective tissue disease.

Three categories of ascending aortic biopsy controls consisted of (1) positive controls: 15 patients with Marfan syndrome or annuloaortic ectasia12-14; and (2) negative controls: 11 patients undergoing CABG, 1 transplant donor, and 10 patients with acquired trileaflet calcific aortic stenosis. Seven pulmonary trunk negative
controls were from patients undergoing CABG. Ascending aortic biopsies from patients with bicuspid aortic stenosis or regurgitation (Table 1) were compared with each other and with biopsies from acquired calcific aortic stenosis of inherently normal trileaflet valves.

No pregnancies occurred among 49 females with Marfan syndrome, annuloaortic ectasia, bicuspid aortic valve, or aortic coarctation. Systemic blood pressure (average of 3 sphygmomanometer determinations) in aortic biopsy patients without coarctation was systolic, 92 to 130 mm Hg (mean, 115 ± 6 mm Hg) and diastolic, 60 to 82 mm Hg (mean, 72 ± 6 mm Hg). All control subjects and all study patients except those with coarctation had normal systemic arterial pressure for age. Four biopsied infants and 3 necropsied adults with truncus arteriosus had systemic arterial pressure in the truncus; the infants had wide pulse pressures.

Aorta and Pulmonary Trunk

Preoperative ascending aortic, paracoarctation aortic, and pulmonary trunk diameters were determined by 2D echocardiography, CT, or MRI.

### TABLE 1. Aorta: Biopsy Specimens

<table>
<thead>
<tr>
<th>Disease</th>
<th>Normal</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
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<td>21</td>
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<tr>
<td>Annuloaortic ectasia</td>
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<td>0</td>
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<td>Bicuspid aortic stenosis</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bicuspid aortic regurgitation</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Paracoarctation aorta</td>
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<tr>
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<tr>
<td>Truncus arteriosus type I</td>
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<td>Initial operation</td>
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<td>0</td>
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<td>Conduit replacement</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Complete transposition of great arteries, Jatene operation</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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<tr>
<td>DOLV, pulmonary stenosis, DAR</td>
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<td>0</td>
</tr>
<tr>
<td>Single ventricle, pulmonary stenosis, DAR</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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<tr>
<td>VSD, DAR</td>
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<td>0</td>
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<tr>
<td>Double aortic arch, DAR</td>
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<td>0</td>
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</tbody>
</table>

DORV indicates double-outlet right ventricle; DAR, dilated aortic root; and DOLV, double-outlet left ventricle.

### Techniques and Morphological Analyses

Biopsies were examined by LM and EM; necropsy specimens by LM. LM specimens were fixed in formaldehyde, embedded in paraffin, and stained with hematoxylin and eosin. Elastic Van Gieson stain (low power, ×4; high power, ×10) was used for examining elastic fibers, trichrome stain for collagen, and Hale’s colloidal iron for ground substance. Fresh EM tissue was fixed in 2.5% glutaraldehyde and 2% paraformaldehyde, postfixed with osmium tetroxide, and embedded in an epoxy resin. Semithin sections were prepared with a polychromatic stain for screening and selection. Ultrathin sections were stained with uranyl acetate and lead citrate. Electron micrographs were prepared on a Zeiss EM 109 microscope.

A grading system consisted of negative controls (presumed normal) and grades 1, 2, and 3, the latter representing positive controls from Marfan syndrome or annuloaortic ectasia. Grades were based on LM and EM analyses of medial smooth muscle, elastic fibers, collagen, and ground substance (Figures 1 to 4) as described in the legends. All specimens were interpreted by 1 histologist and electron microscopist (S.M.B.) who was blinded to the clinical data.

### TABLE 2. Pulmonary Trunk: Biopsies and Necropsy Specimens

<table>
<thead>
<tr>
<th>Disease</th>
<th>Normal</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
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<tbody>
<tr>
<td>Controls</td>
<td>6</td>
<td>6</td>
<td>6</td>
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<td>Fallot’s tetralogy, absent pulmonary valve, aneurysmal PT</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>Pulmonary stenosis, aneurysmal PT</td>
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<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary artery aneurysm extirpated specimen</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single ventricle, pulmonary atresia, focal RPA aneurysm</td>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary trunk-necropsy specimens (LM)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>VSD Eisenmenger</td>
<td>6</td>
<td></td>
<td>3</td>
<td>3*</td>
</tr>
<tr>
<td>Fallot’s tetralogy, large BT shunt, PVD, ruptured aneurysmal PT</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Complete TGA, VSD, PVD, palliative Mustard</td>
<td>2</td>
<td></td>
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</tr>
</tbody>
</table>

PT indicates pulmonary trunk; RPA, right pulmonary artery; and BT, Blalock-Taussig.

*One ruptured aneurysmal PT.
The UCLA Human Subjects Protection Committee approved the protocol. Surgical specimens were obtained after informed consent.

### Results

Normal aortic and pulmonary trunk medial smooth muscle, elastin, collagen, and ground substance are shown in Figures 1, 2, and 3. Relatively large LM samples were superior for quantitative analyses. EM was superior for qualitative substructural analyses.

**Ascending Aorta and Paracoarctation Aorta**

Media above a bicuspid aortic valve was consistently abnormally and identical whether the valve was stenotic or incompetent (Table 1). Ascending aortic media associated with acquired calcific stenosis of inherently normal trileaflet valves was identical with negative controls. All paracoarctation biopsies had medial abnormalities (Table 1), the degree of which was identical in proximal and distal segments, including in a 3-week-old neonate. In Fallot’s tetralogy with pulmonary stenosis or atresia, ascending aortic media was grade 2 or 3 (Figures 1, 2, and 3) (Tables 1 and 3). One such patient, 73 years old, had a 5.4-cm ascending aorta that fragmented during surgery and had an abdominal aortic aneurysm that had previously been operated on. Neonates with complete transposition of the great arteries (TGA) had grade 2 to 3 medial abnormalities in normal-sized ascending aortas (Table 1). A 14-year-old boy with a restrictive perimembranous ventricular septal defect (VSD) had a 5.6-cm ascending aorta with grade 3 medial abnormalities (Table 1).

### Paracoele

Necropsy specimens in adults with Fallot’s tetralogy and dilated ascending aortas had grade 2 to 3 medial abnormalities (Table 3). A phenotypically normal female with an Eisenmenger VSD ruptured a normal-sized ascending aorta (Table 1). Ascending aortic media associated with acquired calcific stenosis of inherently normal aortic valves was identical proximal to the coarctation aorta2 and the ascending aorta above a bicuspid aortic valve (stiffness).

### Pulmonary Trunk

Grade 3 medial abnormalities were found in biopsies of aneurysmal pulmonary trunks in Fallot’s tetralogy with absent pulmonary valve and in mobile pulmonary valve stenosis (Table 2). A patient with a single ventricle and pulmonary atresia had grade 3 medial abnormalities in a focal right pulmonary artery aneurysm (Table 2). One patient with an atrial septal defect had grade 3 medial abnormalities in a dilated volume-overloaded normotensive pulmonary trunk.

Pulmonary trunk necropsy specimens disclosed grade 2 or 3 medial abnormalities in patients with pulmonary vascular disease (PVD) and VSD or complete TGA (Table 2). Two such patients had pulmonary trunk aneurysms, 1 of which fatally ruptured (Table 2). One patient with Fallot’s tetralogy and PVD induced by a large Blalock-Taussig shunt suffered a fatal rupture of an aneurysmal pulmonary trunk with grade 3 medial abnormalities (Table 2).

**Truncus Arteriosus**

Biopsies at initial repair (infants 4 to 6 months old) disclosed grade 2 or 3 medial abnormalities (Table 1); an additional patient had grade 3 medial abnormalities at age 5 years (re-repair) (Table 1). Necropsy specimens in adults with truncus arteriosus and PVD disclosed grade 3 medial abnormalities (Table 3).

### Discussion

In 1928, Gsell coined the term “medionecrosis,”15 and in 1930, Erdheim described “medionecrosis aortae idiopathica-cystica.”16 Cystic medionecrosis soon became part of the medical vocabulary, but the designation “cystic” is open to question because the “cysts” represent noncystic medial structural faults, and necrosis is seldom encountered.

Current interest has shifted to specific medial constituents—smooth muscle, and extracellular matrix that consists of ground substance, a hydrated gel composed of glycosaminoglycans, proteoglycans, and adhesive glycoproteins in which elastic fibers and collagen are embedded—and the role of these constituents in the structural and functional integrity of great arterial walls.17–19 Smooth muscle governs vasodilation and constriction. Elastin, with its low elastic modulus,9 is readily deformable, permitting phasic distension and recoil in response to pulsatile flow. Collagen provides inert strength (stiffness).

The ultimate expression of great arterial medial abnormalities is Marfan syndrome or anulooaortic ectasia, the prototypical extremes12–14 (positive controls). In 18 varieties of CHD (Tables 1 to 3), abnormalities that were qualitatively similar and occasionally quantitatively identical to the positive controls were found in thoracic aortas and pulmonary trunks. Published data on the proximal and distal paracoarctation aorta2 and the ascending aorta above a bicuspid aortic valve5 were reexamined and extended by use of EM and LM with special stains.

**Paracoarctation Aorta**

Medial abnormalities were identical proximal to the coarctation (high-pressure, low-velocity zone) and distal (low-pressure, high-velocity zone)6 (Table 1), implying that the abnormalities were not hemodynamically determined. An inherent pathogenesis is also in accord with observations that (1) in fetuses with a widely patent ductus arteriosus, mechanical forces do not impinge on what is destined to become the postnatal paracoarctation aorta and (2) grade 3 medial abnormalities were present in the paracoarctation aorta in the third week of life (Table 1) and have been reported within 24 hours postpartum.2

**Ascending Aortic Dilatation**

Dilatation above stenotic aortic valves has been attributed to poststenotic turbulence, but ascending aortic turbulence generated by discrete congenital subaortic stenosis is accompanied by no more than moderate aortic dilatation,20 and
acquired calcific stenosis of inherently normal trileaflet aortic valves is accompanied by normal media and no more than moderate dilatation, discounting turbulence per se as the cause of dilatation. The ascending aorta above a bicuspid valve is dilated whether the valve is stenotic, incompetent, or functionally normal.3,4 Medial abnormalities are identical irrespective of the functional state of the valve (Table 1), an observation favoring an inherent medial fault.

In Fallot’s tetralogy, ascending aortic dilatation varies inversely with the degree of right ventricular outflow tract obstruction, being largest with pulmonary atresia.21 Four variables potentially influence ascending aortic size: (1) abnormal morphogenesis that results in unequal division of the fetal truncus, favoring the aorta; (2) volume overload implicit in the biventricular aorta; (3) aortic regurgitation that augments volume overload and introduces pulsatile flow that may facilitate dilatation21,22; and (4) an intrinsic medial fault (Table 1) (Figure 5B).

In double-outlet right or left ventricle, single ventricle, or tricuspid atresia with pulmonary stenosis, the volume-overloaded ascending aorta was dilated and contained grade 2 or 3 medial abnormalities (Table 1). In double aortic arch, grade 2 medial abnormalities in a dilated ascending aorta (Table 1) may have been inherent.

Normal-Sized Ascending Aorta
In VSD with the Eisenmenger syndrome, a normal-sized ascending aorta may harbor inherent medial abnormalities.5 In 1 such patient, a normal-sized ascending aorta with grade 3 medial abnormalities fatally ruptured (Table 3). A surprising variation on this theme was a 14-year-old boy with a restrictive VSD and a 5.6-cm ascending aorta that contained

Figure 1. LM ascending aortic biopsies, elastic van Gieson (EVG) stain. Low power (×4), left column. Entire cross section of aortic wall is visualized (full thickness transmural). a indicates adventitia. Elastic tissue is better identified with high power (×10), right column. A and B, Normal (negative control). Aortic media with closely packed, long parallel arrays of intact elastic fibers. C and D (grade 1), mild elastic fiber fragmentation that at low power appears as patchy pale zones but at high power as gaps in continuity along elastic fibers. E and F (grade 2), widespread elastic fiber fragmentation. G and H (grade 3) (positive control), complete loss of elastic fibers involving large areas of media.
grade 3 medial abnormalities without apparent cause (Table 1).

The ascending aorta in complete TGA is usually normal-sized. However, 8 neonates had grade 2 to 3 ascending aortic medial abnormalities (Table 1) similar to those reported, suggesting an inherent pathogenesis.

**Independent Variables**

Pregnancy, age, and systemic hypertension influence the structure of aortic media. Pregnancy is accompanied by fragmentation of elastic fibers, a decrease in mucopolysaccharides, and an increase in smooth muscle. To what extent these changes normalize after delivery is unknown. Because increasing numbers of female patients with CHD now reach reproductive age, it is appropriate to ask whether gestational changes are additive to those described here in CHD. With advancing age, ascending aortic elastic fibers fragment, smooth muscle cells decrease, collagen and ground substance increase, distensibility declines, and circumference increases, changes influenced by but occurring independently of vasa vasorum flow or intimal atherosclerosis. In systemic hypertension, abnormalities of elastin and collagen are significantly more prevalent than in normotensive subjects of comparable age. Experimentally induced systemic hypertension is accompanied by an increase in synthesis and accumulation of thoracic aortic collagen. Coarctation hypertension is accompanied by an increase in ascending aortic medial collagen and a decrease in smooth muscle (increased stiffness) that may persist after successful repair and coincide with ascending aortic abnormalities of a coexisting bicuspid aortic valve.

**Nonhypertensive Pulmonary Trunk Dilatation**

Mobile congenital pulmonary valve stenosis is associated with conspicuous dilatation of the pulmonary trunk, but dysplastic pulmonary valve stenosis is accompanied by relatively little dilatation despite equivalent poststenotic turbulence, discounting turbulence per se as a pivotal factor in dilatation. Pulmonary trunk dilatation above a mobile stenotic pulmonary valve may be related to the morphology of that specific type of congenitally malformed valve rather than to its functional state, analogous to the proposed relationship between a bicuspid aortic valve and dilatation of the ascending aorta. Pulmonary trunk aneurysms are occasionally asso-
ciated with mobile pulmonary valve stenosis, and fragmentation of medial elastic fibers with mucoid degeneration has been found in these aneurysms (Table 2). One patient underwent pulmonary trunk aneurysmectomy with valve replacement 15 years after valvotomy for mobile congenital stenosis; there were grade 3 medial abnormalities in the aneurysmal pulmonary trunk (Table 2).

When the Jatene arterial switch operation was preceded by a pulmonary artery band, grade 2 to 3 medial abnormalities were subsequently found in the pulmonary trunk (neoaorta). Assuming that the pulmonary trunks were initially normal, these postband medial abnormalities were probably acquired.

In Fallot’s tetralogy with absent pulmonary valve, the pulmonary trunk and proximal branches dilate massively. Regurgitant volume in utero is returned to the pulmonary trunk during each right ventricular systole, phasically distending the central pulmonary arteries, more so when egress is curtailed by agenesis of the ductus arteriosus. These aneurysmal pulmonary trunks had grade 3 medial abnormalities (Table 2) attributed to abnormal flow patterns originating in utero.

One patient with a large left-to-right shunt at the atrial level had grade 3 medial abnormalities in a dilated normotensive pulmonary trunk.

**Hypertensive Pulmonary Trunk Dilatation**

When pulmonary hypertension dates from birth, pulmonary trunk histology is initially indistinguishable from that of the ascending aorta, but when hypertension is acquired after birth, the pulmonary trunk differs significantly from the ascending aorta. Before 1 year of age, medial abnormalities in hypertensive pulmonary trunks associated with nonrestrictive VSDs are absent, but they are consistently present after age 5 years. Patients with VSD and the Eisenmenger syndrome had grade 3 medial abnormalities in dilated hypertensive pulmonary trunks, 2 of which were aneurysmal (Figure 5A), 1 of which fatally ruptured (Table 2). Complete TGA with nonrestrictive VSD was associated with grade 2 medial abnormalities in hypertensive pulmonary trunks (Table 2). A patient with Fallot’s tetralogy and PVD induced by an oversized Blalock-Taussig shunt suffered a rupture of a hypertensive aneurysmal pulmonary trunk with grade 3 me-
Truncus arteriosus is neither an aorta nor a pulmonary trunk, differing from a large aorta with pulmonary atresia or a large pulmonary trunk with aortic atresia, both of which have an aortopulmonary septum.15,36 Medial abnormalities in neonates and infants with truncus arteriosus (Table 1) may be inherent, albeit facilitated by systemic arterial pressure, volume overload, and a wide pulse pressure. In adults with truncus arteriosus and PVD (Table 3), medial abnormalities must be considered in light of abnormalities in neonates and infants (Table 1).

**Significance of the Observations**

It is uncertain whether medial abnormalities, even in neonates and young infants, are inherent or acquired, whether and to what degree coexisting CHD plays a causal or facilitating role, or to what extent the abnormalities are responses to dilatation per se. Nevertheless, the range, prevalence, degree, and potential risks, including cardiac surgical risks, posed by these abnormalities are matters that warrant emphasis.

**Pathogenesis**

Assuming that some medial abnormalities in CHD are inherent, do the abnormalities reflect 1 or more genetic defects?3,7 Might the neural crest be linked to medial abnormalities in conotruncal malformations?7 Marfan syndrome is characterized by a defect in the chromosome 15 gene that codes for fibrillin-1, in the absence of which elastin is more readily degraded by metalloproteinases.12 The genetic fault in Marfan syndrome seems to impair aortic medial elastic fibers more extensively than the observed impairment in CHD, because the incidence of ascending aortic dissection or rupture is higher in Marfan syndrome or annuloaortic ectasia13,14 than in CHD patients with aortic root dilatation. Our data set the stage for pathogenetic studies, including morphometric analyses8 and immunoreactivity for matrix metalloproteinases, which are etiologically important in abdominal aortic aneurysms17–19 and in certain thoracic aortic aneurysms.13

**Limitations**

We had limited access to biopsies from dilated pulmonary trunks accompanying low–resistance, high-flow atrial septal
defects, which are now closed via minithoracotomy, and limited access to dilated pulmonary trunks associated with mobile pulmonary valve stenosis, which is now treated by balloon valvuloplasty.

Conclusions
A hitherto unrecognized prevalence of great arterial medial abnormalities of smooth muscle, elastic fibers, collagen, and ground substance was found in 18 types of CHD encompassing a wide age range. Aortic medial abnormalities may be associated with or predispose to dilatation, aneurysm, and rupture and are potential cardiac surgical risks. Pulmonary trunk medial abnormalities may be associated with or predispose to dilatation and aneurysm formation in mobile pulmonary valve stenosis or Fallot’s tetralogy with absent pulmonary valve. Aneurysmal hypertensive pulmonary trunks may rupture and are risks during lung transplantation.

Three important questions remain: whether great arterial medial abnormalities are inherent or acquired, whether and to what extent CHD plays a causal or a facilitating role, and whether and to what extent genetic determinants are operative.

References
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