Extramural Coronary Arteries in Adults With Cyanotic Congenital Heart Disease

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Dilatation and tortuosity of extramural coronary arteries are prevalent in cyanotic congenital heart disease. Two pathogenetic variables are operative, namely endothelial vasodilator substances and medial structural abnormalities. ©2004 by Excerpta Medica, Inc.

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Dilatation and tortuosity of coronary arteries in cyanotic congenital heart disease have been known for decades, but the incidence and pathogenesis remain to be established.

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In 1955, Aitchison et al[1] published photographs of unusually large tortuous coronary arteries in a 34-year-old man with cyanotic congenital heart disease (CCHD).[1] In 1966, Bjork[2] applied the term "coronary ectasia" to "a previously undescribed anomaly characterized by marked dilatation and tortuosity of the coronary arteries." In 1968, Perloff et al[3] reported aneurysmal dilatation of the coronary arteries in a 38-year-old cyanotic woman, but no mention was made of mural histopathology. These investigators postulated that: "Normal myocardial nutritional requirements demand maximal oxygen extraction from coronary arterial blood. When aortic saturation is low, maximal extraction may not provide the myocardium with adequate oxygen, a deficit that might be overcome by increased coronary blood flow. Large flow acting over a protracted period of time could result in dilatation and tortuosity."[3] In 1971, Arias-Stella and Topilsky[4] described coronary artery dilatation and tortuosity in hypoxemic erythrocytotic adults acclimatized to high altitude, implying that the coronary abnormalities were responses to hypoxemia and erythrocytosis per se. Studies of conduit arteries subsequently disclosed a direct relation between perfusate viscosity and arterial diameter, and showed that an increase in flow-mediated shear stress at the luminal surface resulted in elaboration of endothelial vasodilator substances.[5] The role of nitric oxide (NO) in shear-induced vasodilatation of human conductance arteries is now well established.[6,7] Increased endothelial shear stress of the erythrocytotic perfusate in CCHD provokes elaboration of NO and prostaglandins, but to what degree of the coronary dilatation is in response to the endothelial mechanism alone? Great arterial walls in congenital heart disease dilate out of proportion to hemodynamic or developmental expectations and harbor medial abnormalities.[8] Are there coexisting medial structural faults in aneurysmal ectatic coronary arteries?

TABLE 1 Primary Diagnosis in Patients With Cyanotic Congenital Heart Disease

Primary Diagnosis	No. of Patients
Tetralogy of Fallot	12
With pulmonary atresia	5
Ventricular septal defect	14
Tricuspid atresia	10
Single ventricle	9
Truncus arteriosus	5
d-Transposition	4

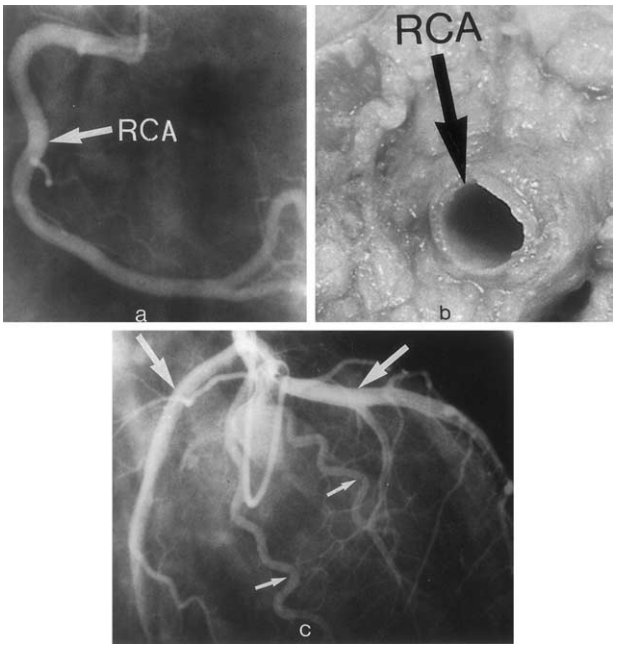

FIGURE 1. ***(A)*** **Selective coronary arteriogram illustrating moderate dilatation of the right coronary (RCA) in a 46-year-old cyanotic man with Eisenmenger's syndrome.** ***(B)*** **Necropsy specimen illustrating moderate dilatation of the RCA in a 38-year-old cyanotic man with Eisenmenger's syndrome. Atheromas were not detected in any of the coronary arteries;** ***(C)*** **Selective left coronary arteriogram from a 53-year-old cyanotic man with Eisenmenger's syndrome. The circumflex and left anterior descending arteries** ***(large upper arrows)*** **are moderately dilated; the diagonal branches** ***(small lower arrows)*** **are moderately dilated and tortuous. At necropsy 18 months later, the coronary arteries were atheroma free.**

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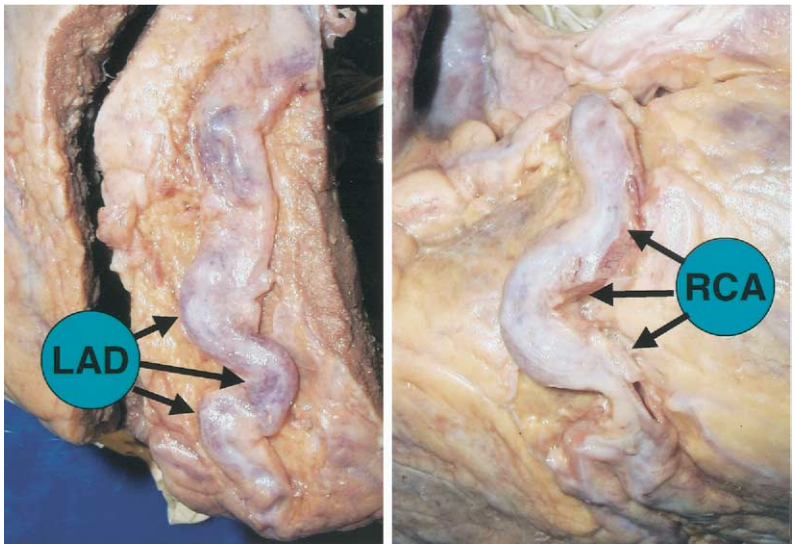

FIGURE 2. Gross example of dilated ectatic tortuous coronary arteries in a 43-year-old cyanotic woman with Eisenmenger's syndrome. LAD = left anterior descending artery; other abbreviation as in Figure 1.

Our study of extramural coronary arteries in CCHD consisted of 2 parts, namely, coronary angiography in 59 adults and coronary histopathology in 6 adults. The coronary angiograms were selective in 29 of 59 patients, and followed aortic root injection in 39 of 59 patients. The study included 25 women (aged 34 to 54 years, mean 43) and 34 men (aged 36 to 56 years, mean 41). Systemic arterial oxygen saturations were 74% to 83% (mean 79%) and hematocrit measurements 59% to 70% (mean 67%). The original coronary angiograms were interpreted by 1 co-author (JSC) (Table 1). Reinterpretations were by 1 co-author (JKP) without knowledge of the original interpretations. The same criteria were used to characterize coronary arteries in the original interpretations and in the reinterpretations: (1) normal in size and configuration, (2) nondilated but tortuous, (3) moderately dilated but nontortuous, (4) both moderately dilated and tortuous, and (5) aneurysmally dilated. Although the size of normal coronary arteries in adults has been studied, no method(s) have been agreed upon for quantifying the degree of dilatation.[9–11]

Necropsy specimens of coronary arteries from 6 adults with CCHD were sectioned along their epicardial courses at proximal, mid-, and distal sites, and examined histologically with hematoxylin/eosin, Masson's trichrome stain for collagen, and smooth muscle, elastica von Gieson for elastic tissue, and alcian blue for extracellular matrix (acid mucopolysaccharide). Multiple sections of each coronary artery were available in at least 2 to 5 slides. Medial smooth muscle cell loss, increased medial collagen, increased mucopolysaccharides, disruption of internal elastic lamina, and intimal fibromuscular hyperplasia were graded as 1 = focal mild; 2 = circumferential mild; and 3 = circumferential prominent.

Control specimens of normal coronary arteries from 4 adults with dilated cardiomyopathy were sectioned along their epicardial courses at the same locations as in patients with CCHD. Microscopic examinations, stains, age range, and gender distribution were similar in both groups.

The coronary arteries were angiographically normal in 8 patients with CCHD, nondilated but tortuous in 10, nontortuous but moderately dilated in 12, moderately dilated and tortuous in 16, and both aneurysmally dilated and tortuous in 13 (Figure 1). None of the 59 arteriograms revealed coronary atherosclerosis.

Coronary arteries in the 6 CCHD necropsy specimens were grossly ectatic and tortuous (Figure 2). Histologic examination disclosed loss of medial smooth muscle cells (mean value 1.4), increased medial collagen (mean value 1.8), increased medial and intimal extracellular matrixes (mean value 1.3), disruption of internal elastic lamina (mean value 1.5), and focal intimal fibromuscular hyperplasia (mean value 1.75) (Figure 3). Atherosclerosis was absent except for small foci in occasional sections. Histology in the 4 control subjects with normal coronary arteries disclosed no loss of smooth muscle cells, no increase in medial collagen, a single internal elastic lamina, and occasional foci of mild fibromuscular intimal hyperplasia (Figure 4).

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What pathogenetic mechanism(s) might account for dilatation and/or tortuosity in such a substantial number of patients with CCHD (86%)? Why do these changes variously express themselves as dilatation, tortuosity, or combinations thereof? Are moderate dilatation and aneurysmal ectatic dilatation 2 ends of a pathogenetic spectrum, or are different mechanisms operative?

Shear stress-induced dilatation is well-supported by published data.[5] In CCHD, endothelial vasodilator NO and prostaglandins are believed to be elaborated in response-increased endothelial shear stress of the viscous erythrocytotic perfusate.[6,7] Consistent with these suppositions is the relation between red cell mass, whole blood viscosity, and the angiographic size of the extramural coronary arteries. In patients with dilated and/or tortuous coronary arteries, hematocrit measurements were 65% to 70%, whereas the 14% with normal coronary arteries had hematocrit measurements of 59% to 61%. Increased laminar shear stress upregulates the expression of endothelial NO synthase.[6,7] The paucity of coronary atherosclerosis in CCHD permits unimpaired vasodilatation, and the upregulated NO, together with hypoxemia, hypocholesterolemia, and hyperbilirubinemia, are antiatherogenic.

Is aneurysmal dilatation of the coronary a response to shear stress-induced vasodilatation alone, or do

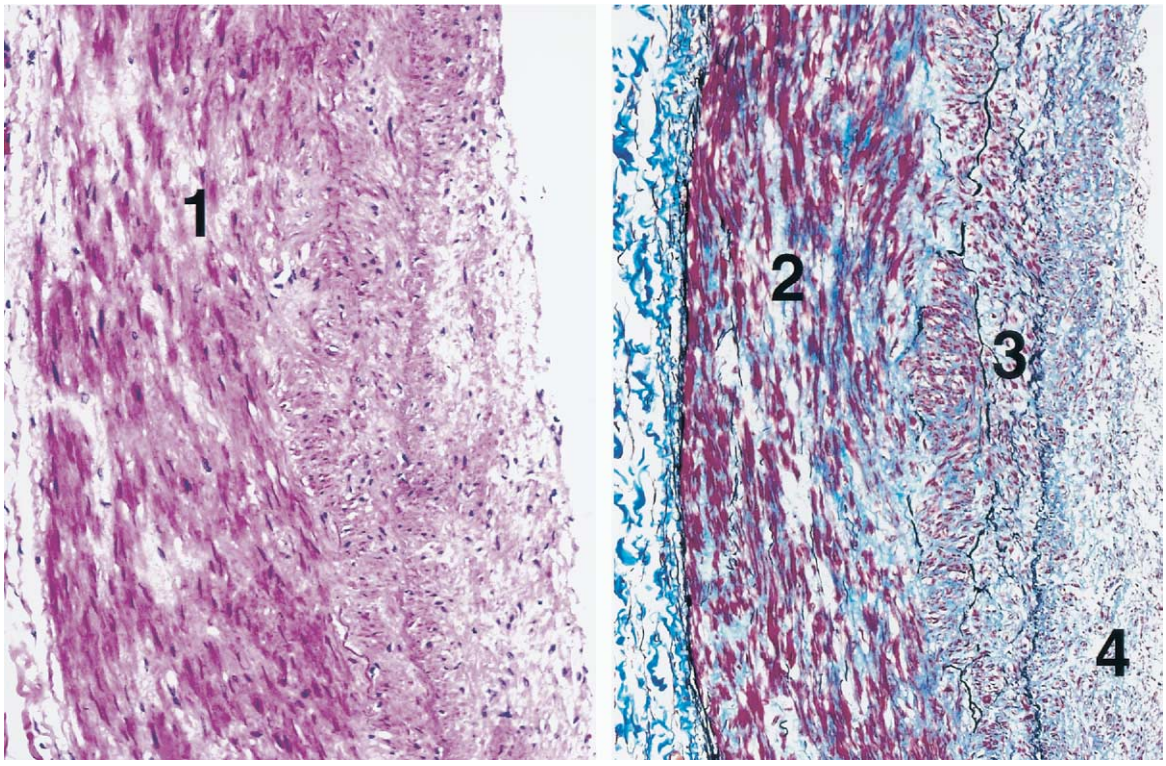

FIGURE 3. Dilated ectatic tortuous coronary artery from the cyanotic patient referred to in Figure 2 showing: 1 = loss of medial smooth muscle cells; 2 = increased medial collagen; 3 = duplication of internal elastic lamina; and 4 = fibromuscular intimal hyperplasia. *Left,* hematoxylin/eosin stain; *right,* Masson's trichrome/elastic stain right (× 200, reduced by 31%).

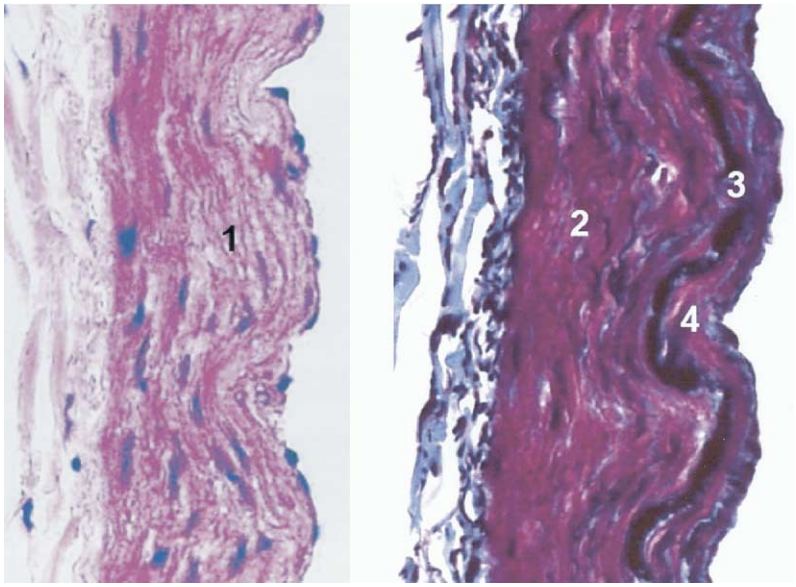

FIGURE 4. Normal coronary artery showing: 1 = no loss of medial smooth muscle cells; 2 = no increase in medial collagen; 3 = single internal elastic lamina; and 4 = mild focal fibromuscular intimal hyperplasia. *Left,* hematoxylin/eosin stain; *right,* Masson's trichrome/elastic stain right; × 200, reduced by 39%).

medial structural abnormalities (Figure 3) augment dilatation by mural attenuation? Are medial structural abnormalities late consequences of endothelial gene up/down regulation secondary to endothelial shear stress, or do they reflect developmental abnormalities?[8]

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