Cyanotic Congenital Heart Disease and Coronary Artery Atherogenesis

Alistair Fyfe, MD, PhD[a], Joseph K. Perloff, MD[b,*], Koichiro Niwa, MD[c], John S. Child, MD[b], and Pamela D. Miner, MN, NP[b]

Hypoxemic erythrocytotic residents of high altitudes lack coronary atherosclerosis and have low cholesterol levels. It was postulated that hypoxemic erythrocytotic adults with cyanotic congenital heart disease (CCHD) might be analogous. The incidence of coronary atherosclerosis in this patient population has not been established, and hypocholesterolemia has not previously been recognized. Accordingly, 279 patients were divided into 4 groups: group A: 143 cyanotic patients not operated on (54 men and 89 women, aged 18 to 69 years); group B: 47 cyanotic patients (28 men and 19 women rendered acyanotic by operation at age 22 to 69 years); group C: 41 acyanotic patients not operated on (22 men and 19 women, aged 22 to 75 years); and group D: 48 patients acyanotic before and after operation (24 men and 24 women, aged 21 to 70 years). Coronary arteries were studied angiographically in 59 patients and at necropsy in 5 subjects aged 37 to 56 years. Total cholesterol was <160 mg/dl in 58% of group A, 52% of group B, 10% of group C, and 12% of group D ($p < 0.000001$, chi-square analysis). Angiograms disclosed dilated coronary arteries without obstruction. Necropsy disclosed ectatic coronary arteries with structural abnormalities of the media. In conclusion, this study provides the first quantitative and qualitative data on antiatherogenic changes in lipoproteins in adults with CCHD. The coronary arteries are atheroma free because hypocholesterolemia acts in concert with the antiatherogenic properties of upregulated nitric oxide, hyperbilirubinemia, hypoxemia, and low platelet counts. The persistence of hypocholesterolemia after the surgical elimination of cyanosis suggests a genetic determinant. **(Am J Cardiol 2005;96:283–290)**

Hypoxemic erythrocytotic residents of high altitudes are hypocholesterolemic and devoid of clinical and necropsy evidence of coronary artery atherosclerosis.[1,2] We hypothesized that hypoxemic erythrocytotic adults with cyanotic congenital heart disease (CCHD) might be analogous. However, the incidence of coronary atherosclerosis has not been established in this patient population, and hypocholesterolemia has not previously been recognized. Accordingly, we studied 279 patients from the Ahmanson/UCLA Adult Congenital Heart Disease Center.

Methods

Patient population: The University of California, Los Angeles, institutional review board approved the protocol. Four groups were included in the study (Figure 1): group A: 143 cyanotic patients not operated on (54 men and 89 women, aged 18 to 69 years [mean 36 ± 11], hematocrit [Coulter Electronics, Inc., Hialeah, Florida] 57% to 73% (mean 61 ± 8%], systemic arterial O_2 saturation 74% to 83% [mean 79 ± 3%]); group B: 47 cyanotic patients (28 men and 19 women rendered acyanotic by operation at age 22 to 69 years [mean 38 ± 12], mean postoperative follow-up 16.9 years, postoperative hematocrit 37% to 55% [mean 41 ± 5%]); group C: 41 acyanotic patients not operated on (22 men and 19 women, aged 22 to 75 years [mean 44 ± 15], hematocrit 32% to 44% [mean 41 ± 4%]); and group D: 48 patients acyanotic before and after operation (24 men and 24 women, aged 21 to 70 years [mean 41 ± 4], mean postoperative follow-up 15 years, hematocrit 35% to 46% [mean 42 ± 3%]).

No patient had a myeloproliferative disease, none was malnourished, none had ever taken a cholesterol-lowering medication, and all were born and raised at sea level.

Coronary arteries: Arteriograms were studied in 68 patients in group A, 29 after selective coronary angiography and 39 after aortic root injections. All initial studies were done and interpreted by the same experienced cardiologist (JSC).

[a]Dallas Heart Group, Dallas, Texas; [b]Ahmanson/UCLA Adult Congenital Heart Disease Center, University of California, Los Angeles, School of Medicine, Los Angeles, California; and the [c]Department of Pediatrics, Chiba Cardiovascular Center, Chiba, Japan. Manuscript received November 15, 2004; revised manuscript received and accepted March 4, 2005.

* Corresponding author: Tel.: 310-825-2019; fax: 310-825-6346.
E-mail address: josephperloff@earthlink.net (J.K. Perloff).

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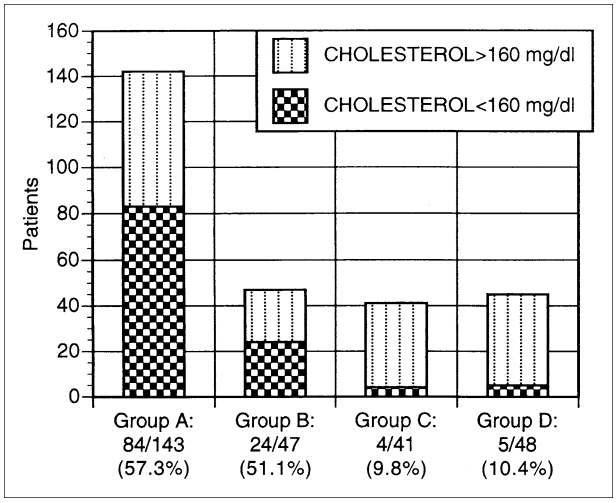

Figure 1. Incidence of nonfasting total low cholesterol level. Group A: cyanotic patients not operated on; group B: acyanotic patients before and after operation; group C: acyanotic patients not operated on; group D: acyanotic patients before and after operation.

Reinterpretations were done by a separate experienced cardiologist (JKP) without knowledge of original angiographic interpretations with which the blinded reinterpretations were compared.

All 29 selective coronary angiograms and 30 of 39 aortic root angiograms were of high quality. These 59 angiograms included 25 women aged 38 to 54 years (mean 43 ± 3) and 24 men aged 36 to 56 years (mean 41 ± 4). Gross and histologic examinations of the coronary arteries were performed in 5 necropsy patients.

Serum cholesterol levels: Nonfasting total cholesterol values were retrieved from our computer-stored data bank. Blood samples were drawn in a sitting or supine position to eliminate the potential effects of posture on cholesterol determinations. Because 160 mg/dl represented the 10th percentile in the Framingham Study,[3] total cholesterol <160 mg/dl was considered low. Directly measured low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined in 57 of 82 hypocholesterolemic patients. Fasting lipoprotein levels were determined in 20 of 82 patients.

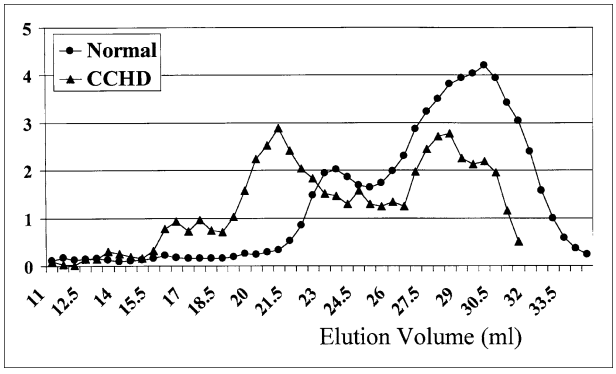

Figure 2. Cholesterol FPLC profile in 4 fasting normal subjects and 4 fasting patients in group A.

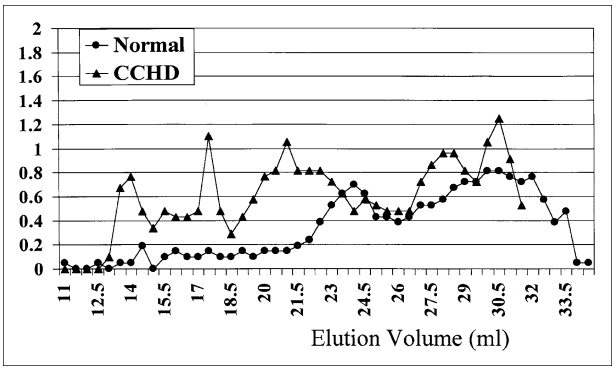

Figure 3. Triglyceride FPLC profile in 4 fasting normal subjects and 4 fasting patients in group A.

Fast protein liquid chromatography (FPLC) analysis: To determine whether any lipoprotein classes were under-represented in the plasma of hypocholesterolemic patients with CCHD, 0.4 ml of fasting plasma was separated using gel filtration chromatography with 2 Superose 6 columns (Pharmacia Corporation, Peapack, New Jersey) connected in series. Fractions of 0.5 ml were collected at 0.5 ml/min. Cholesterol (Figure 2) and triglycerides (Figure 3) were measured in each fraction. Aliquots representing very-low-density lipoprotein (VLDL) cholesterol, LDL cholesterol, and HDL cholesterol elution peaks were displayed in 4 patients using 5% to 30% nondenaturing sodium dodecyl sulfate gels. Pooled fractions representing each elution peak were assayed for apolipoprotein-E (apo-E) and apolipoprotein B (apo-B) by immunoblotting using specific monoclonal human antibodies and chemiluminescence.[4] Nuclear magnetic resonance spectroscopy of plasma from 4 patients with CCHD was performed according to published methods[5] and compared with that of 4 acyanotic patients (Figure 4).

Statistical analyses: Comparisons among the 4 groups regarding total cholesterol, LDL cholesterol, HDL choles-

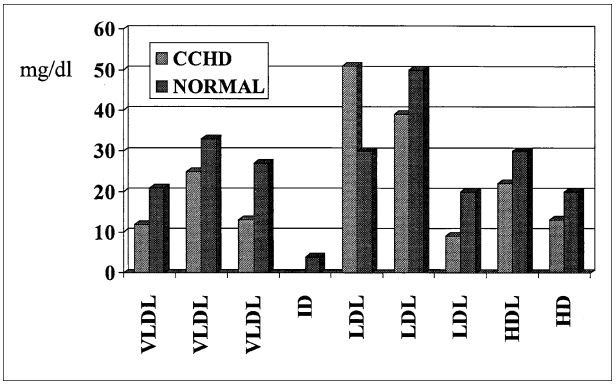

Figure 4. Nuclear magnetic resonance spectroscopic lipoprotein profile in patients with CCHD and normal subjects disclosed large LDL particles and reductions in VLDL and HDL cholesterol.

Table 1
Categories and cardiac diagnoses

Group A: Cyanotic Unoperated (n = 144)	Group B: Acyanotic Postoperative (n = 47)
Atrial septal defect (n = 13)	Double-outlet right ventricle (n = 3)
Ventricular septal defect (n = 36)	Tetralogy of Fallot (n = 20)
Atrioventricular septal defect (n = 10)	Complete transposition of the great arteries (n = 5)
Double-outlet right ventricle (n = 9)	Ebstein's anomaly (n = 3)
Double-outlet left ventricle (n = 2)	Single ventricle (n = 5)
Complete transposition great arteries (n = 12)	Tricuspid atresia (n = 10)
Taussig-Bing anomaly (n = 1)	Total anomalous pulmonary venous connection (n = 1
Ebstein's anomaly (n = 8)	
Patent ductus (n = 3)	
Primary pulmonary hypertension (n = 5)	
Pulmonary atrioventricular fistula (n = 1)	
Single ventricle (n = 10)	
Tricuspid atresia (n = 8)	
Tetralogy of Fallot (n = 19)	
Truncus arteriosus (n = 8)	

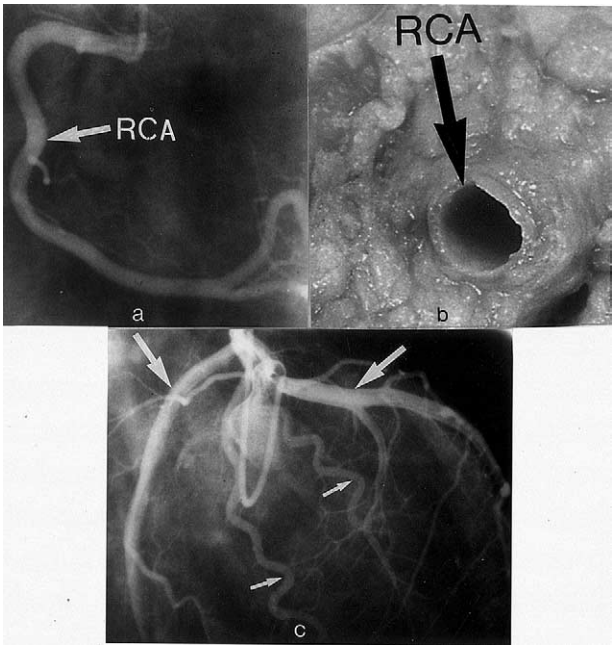

Figure 5. *(A)* Selective right coronary arteriogram from a 46-year-old cyanotic man with ventricular septal defect and Eisenmenger's syndrome. The right coronary artery (RCA) is moderately dilated with no detectable atheroma. *(B)* Necropsy specimen of a markedly dilated RCA in a 38-year-old cyanotic man with truncus arteriosus. Atheroma was not detected in any of the coronary arteries. *(C)* Selective left coronary arteriogram from a 53-year-old cyanotic man with ventricular septal defect and Eisenmenger's syndrome. The circumflex and left anterior descending arteries *(large upper arrows)* are moderately dilated; the diagonal branches *(small lower arrows)* are mildly dilated and tortuous. There was no angiographic evidence of atheroma, and at necropsy 18 months later, all coronary arteries were free of atheroma.

terol, and hematocrit were performed using a completely randomized 1-way analysis of variance (ANOVA) model. A logarithmic transformation was used to achieve a Gaussian distribution. If significant differences were found among groups, the results were subanalyzed using the Tukey-Kramer multiple-comparison procedure and a global 5% significance level. Gender comparisons within each group were based on the standard 2-sample *t* test. The determination of the percentage of patients with total cholesterol <160 mg/dl used the chi-square test for homogeneity. Pearson's product-moment correlation coefficient was calculated between total cholesterol and hematocrit for each group. Values were evaluated using the appropriate *t* test for determining whether a correlation was significantly different from zero. Total cholesterol was compared qualitatively to Framingham controls aged 30 to 49 years.[3] Means ± SDs were used as summary statistics. A 5% significance level was used throughout.

Table 2
Categories and cardiac diagnoses

Group C: Acyanotic Unoperated (n = 41)	Group D: Acyanotic Pre- and Postoperatively (n = 48)
Atrial septal defect (n = 10)	Atrial septal defect (n = 12)
Atrioventricular septal defect (n = 2)	Lutembacher's syndrome (n = 1)
Bicuspid aortic stenosis (n = 6)	Ventricular septal defect (n = 6)
Subaortic stenosis (n = 3)	Atrioventricular septal defect (n = 2)
Coarctation of aorta (n = 2)	Bicuspid aortic stenosis (n = 7)
Anomalous coronary artery (n = 1)	Subaortic stenosis (n = 2)
Congenitally corrected transposition (n = 2)	Coarctation of aorta (n = 10)
Ventricular septal defect (n = 10)	Congenitally corrected transposition (n = 2)
Ebstein's anomaly (n = 1)	Sinus Valsalva rupture (n = 1)
Pulmonary atrioventricular fistula (n = 1)	Pulmonary valve stenosis (n = 4)
Pulmonary valve stenosis (n = 2)	Patent ductus (n = 1)

Results

Congenital malformations were represented by ventricular septal defects in 52 patients and atrial septal defects in 35 (Tables 1 and 2). Cyanotic ventricular septal defects (Eisenmenger's syndrome) were present in 36 of 52 patients; 16 of 52 were acyanotic. Cyanotic atrial septal defects (Eisenmenger's syndrome) were present in 13 of 35 patients; 22 of 35 were acyanotic. Of 36 patients with Eisenmenger's syndrome ventricular septal defects, 16 (44%) had low total cholesterol levels compared with 1 of 15 (6%) who were acyanotic ($p = 0.009$). Even more striking were patients with Eisenmenger's syndrome atrial septal defects, 72% of whom had low total cholesterol compared with 13% who were acyanotic ($p < 0.00001$).

Coronary arteries: There was no evidence of atherosclerosis in 59 coronary arteriograms and in 5 necropsy specimens. Coronary arteries were ectatic and tortuous in 13 of 59 angio-

Table 3
Cholesterol and lipid levels

Group	No. of Patients	Total Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	VLDL Cholesterol (mg/dl)
A	143	162 ± 40 (87–313)	104 ± 38 (11–191)	37 ± 10 (16–67)	24 ± 19
B	47	166 ± 37 (90–260)	108 ± 21 (78–135)	41 ± 9 (28–54)	27 ± 23
C	41	210 ± 46 (119–324)	133 ± 26 (106–177)	54 ± 16 (33–79)	33 ± 34
D	48	195 ± 39 (137–285)	122 ± 25 (79–183)	48 ± 12 (27–66)	29 ± 17
p value (ANOVA; based on log transform)		<0.000001	0.054	0.0007	>0.05

Data are expressed as mean ± SD. Total cholesterol: groups A and B significantly lower than groups C and D (Tukey-Kramer procedure). HDL: groups C and D significantly higher than group A but not B (Tukey-Kramer procedure).

grams, moderately dilated and tortuous in 29 (Figure 5), mildly dilated and tortuous in 11, and normal or mildly dilated in 6. Discrepancies between initial angiographic interpretations and subsequent reinterpretations were confined to mild versus normal in 4 of 59 patients. Necropsy disclosed aneurysmal dilation (ectasia; Figure 5), with the loss of medial smooth muscle cells and increased collagen.

Cholesterol and lipoproteins: Inherently cyanotic patients who were not operated on and inherently cyanotic patients who were rendered acyanotic by operation (groups A and B; Table 1) had significantly lower total cholesterol levels than acyanotic patients not operated on in group C or acyanotic postoperative patients in group D (Table 2; $p < 0.05$ by the Tukey-Kramer multiple-comparison procedure). Total cholesterol was 87 to 313 mg/dl in group A, 90 to 260 mg/dl in group B, 119 to 324 mg/dl in group C, and 137 to 285 mg/dl in group D (Table 3). There was no significant difference in mean total cholesterol between men and women in any group and no significant difference relative to patients' ages (Table 4).

Figure 1 shows the number and percentage of patients in each group with total cholesterol <160 mg/dl. Groups C and D included the 10% with low total cholesterol levels predicted by the Framingham Study.[3] Total cholesterol levels were low in 58% of patients in group A and in 52% of patients in group B compared with inherently acyanotic patients in groups C and D ($p < 0.05$ by chi-square test for homogeneity) and compared with age- and gender-matched normal populations.

Groups A and B (Table 1) had reductions in all cholesterol fractions compared with groups C and D (Table 2). LDL cholesterol levels averaged 30% lower in group A compared with group C, but the differences did not reach global significance ($p = 0.054$ by 1-way ANOVA). HDL cholesterol levels differed among the 4 groups ($p = 0.0007$ by 1-way ANOVA), with levels in groups C and D higher than in group A but not group B (by the Tukey-Kramer multiple-comparison procedure). Triglycerides were first analyzed by 1-way ANOVA, which disclosed no difference among groups ($p = 0.41$ using log-transformed data). Triglyceride levels were then considered according to National Institutes of Health criteria as <250, 250 to 500, and >500 mg/dl. Levels were <250 mg/dl in 88% of group A, 93% of group B, 94% of group C, and 92% of group D. There was no difference in these percentages by chi-square analysis ($p > 0.05$ by simulation of the exact distribution).

Hematocrit versus total cholesterol: There was no significant correlation between hematocrit and total cholesterol (Table 5) for groups A, C, and D, but there was a significant correlation for group B ($r = -0.34$, $p = 0.02$).

FPLC lipoprotein analysis: Figures 2 and 3 are cholesterol and triglyceride elution profiles representing the FPLC separation of lipoproteins from 4 normal controls and 4 patients in group A. Normal fasting cholesterol profiles displayed 2 major peaks (Figure 2). The first to elute were LDL cholesterol, at 24 ml, and HDL cholesterol, at 31 ml; the second to elute was VLDL cholesterol, with the void volume of the system ranging from 12 to 15 ml, as indicated by the small triglyceride peak in this area in controls (Figure 3). Patients in group A had larger, more buoyant particles that eluted earlier, with a peak at 21.5 ml and a reduced

Table 4
Cholesterol (mg/dl), men versus women

Group	No.		Men	Women	p Value (M vs F)
	F	M	Total Cholesterol (mg/dl)	Total Cholesterol (mg/dl)	
A	89	54	164 ± 39 (99–313)	161 ± 42 (87–288)	0.51
B	19	28	159 ± 35 (90–248)	176 ± 39 (125–260)	0.12
C	19	22	208 ± 38 (134–324)	212 ± 55 (119–306)	0.97
D	24	24	198 ± 42 (137–284)	191 ± 36 (139–285)	0.62

Data are expressed as mean ± SD. Log transform was used for *t* tests.

Table 5
Incidence of low cholesterol and total cholesterol versus hematocrit

Group	No. of Patients	Total Cholesterol <160 mg/dl	Hematocrit (%)	p Value	Correlation Between Total Cholesterol and Hematocrit
A	143	82 (57.3%)	59 ± 8 (47–73)	0.83	0.02
B	47	24 (51.1%)	41 ± 5 (27–55)	0.02	−0.34
C	41	4 (9.8%)	41 ± 6 (32–44)	0.90	0.02
D	48	6 (12.5%)	41 ± 4 (35–46)	0.33	0.14
p value (ANOVA)		$<10^{-6}$ (chi-square)	$<10^{-6}$		

Data are expressed as mean ± SD or n (%). Low cholesterol: groups A and B more frequent (chi-square test for homogeneity). Hematocrit: group A significantly higher (Tukey-Kramer procedure).

cholesterol content in the HDL cholesterol peak from 27 to 32 ml (Figure 2). A significantly larger amount of cholesterol was carried in an LDL-sized band eluting from 16 to 19 ml.

Pooled fractions eluting from 12 to 15 ml corresponding to VLDL cholesterol, from 19 to 24 ml corresponding to LDL cholesterol, and from 28 to 30 ml corresponding to HDL cholesterol were separated using nondenaturing gradient bell electrophoresis. LDL cholesterol particles in group A disclosed an apo-E size protein confirmed by immunoblotting. The distribution of HDL fraction apolipoprotein did not differ from HDL cholesterol from controls prepared by FPLC or ultracentrifugation (data not shown). Pooled fractions were immunoblotted for apo-E and apo-B-100, which were detected in normal and CCHD fractions. Small amounts of apo-E were detected only in VLDL cholesterol and HDL cholesterol fractions (data not shown). Nuclear magnetic resonance spectroscopy (Figure 4) confirmed lower levels of VLDL and HDL cholesterol particles and identified the intermediate particle on gel filtration as large LDL cholesterol.

Discussion

Angiographic prevalence of asymptomatic coronary atherosclerosis in healthy young populations based on raised lesions differs from necropsy prevalence based on unraised angiographically occult plaques.[6,7] In a necropsy study of the general population, fatty streaks and raised lesions were present at 15 to 34 years of age, and American Heart Association grade 4 to 5 lesions were present at 30 to 34 years of age.[7] In contrast, our patients in groups A and B, who ranged in age from the fourth to the sixth decade, had neither angiographic nor necropsy evidence of atherosclerosis. It is relevant that hypoxemic erythrocytotic residents of high altitudes have a negligible incidence of clinical coronary artery disease,[1,2] and in 300 necropsies from Cerro de Pasco, Peru (4,375 m higher than sea level), no coronary atherosclerosis was found.[2]

In addition to hypocholesterolemia, 4 co-existing but independent antiatherogenic variables contribute to the low incidence of coronary atherosclerosis in CCHD, namely, hypoxemia, upregulated nitric oxide, hyperbilirubinemia, and low platelet counts.

Hypocholesterolemia: Low total cholesterol levels, defined as <160 mg/dl,[3] occurred in 58% of cyanotic patients not operated on (group A; Figure 1) and persisted after the surgical elimination of cyanosis in 52% (group B; Figure 1). Only 11% of cyanotic patients who were hypocholesterolemic before surgery experienced a postoperative increase in total cholesterol to >160 mg/dl (Figure 1). As predicted by the Framingham Study,[3] 10% of acyanotic patients not operated on (group C) or acyanotic postoperative patients (group D) had total cholesterol levels <160 mg/dl (Figure 1). Hypocholesterolemia primarily reflected reductions in LDL cholesterol, with lesser reductions in VLDL and HDL cholesterol (Figure 4). A few patients in groups A and B had elevated nonfasting cholesterol levels (260 to 313 mg/dl; Table 1). These levels might have been even higher had the patients been acyanotic. There were no apparent differences in family history or dietary habits between these few cyanotic patients with elevated cholesterol levels, and most cyanotic patients whose total cholesterol levels were low.

FPLC gel filtration with cholesterol and triglyceride analysis of the fractions disclosed significant qualitative changes in lipoprotein distribution. These data, together with reductions in LDL and HDL cholesterol, indicate significant reductions in the number of LDL and HDL particles. Postulated reductions in LDL particle number were not reflected in reductions of apo-B, as determined by Coomasie-stained gels or apo-B-100 immunoblotting. HDL proteins were unchanged on Coomasie-stained gels. The FPLC profile suggested that apo-B-100–positive and apo-E–positive large LDL particles predominate in the fasting state.

The major contribution of apo-B–containing lipoproteins to total cholesterol implies the underproduction or overuse of VLDL, intermediate-density lipoprotein (IDL), or LDL as the mechanism responsible for low total cholesterol levels. Underproduction occurs with malnutrition, with mutations in the apo-B protein that lead to reduced VLDL production,[8] and with mutations in the microsomal triglyceride transfer protein that diminish intestinal cholesterol absorption.[9] Overuse has been reported in myeloproliferative disorders.[10,11]

It has virtually been unrecognized that hypoxemic erythrocytotic residents of high altitude have reduced levels of

total cholesterol and LDL cholesterol and elevated levels of HDL cholesterol.[1,2] It has previously been unrecognized that hypoxemic erythrocytotic patients with CCHD may be hypocholesterolemic, as reported herein. Five related variables might account for the hypocholesterolemia in CCHD, namely, cyanosis, hypoxemia, erythrocytosis, and genetic determinants.

Cyanosis and hypoxemia are obligatory but insufficient causes that need not be present at birth. This is consistent with observation that <2 years after sea-level residents ascend to hypoxemic high altitudes, their total cholesterol, LDL cholesterol, and HDL cholesterol levels become the same as those of indigenous high-altitude residents.[1,2] The only difference between hypoxemic erythrocytotic adults with CCHD and hypoxemic erythrocytotic residents of high altitudes is with HDL cholesterol levels, which are slightly reduced in the former but increased in the latter.[2] The hypocholesterolemia of CCHD tends to persist after the surgical elimination of cyanosis and hypoxemia (Figure 1), but it is not known whether high-altitude hypocholesterolemia persists after descent to sea level.

Intrauterine hypoxemia does not influence fetal cholesterol levels.[12] In fetuses <6 months old, maternal cholesterol levels are the major determinants of fetal levels, but in older fetuses, cholesterol levels are independent of maternal levels despite the hypoxemic intrauterine environment.[12]

The relation between oxygen saturation and atherosclerosis in various vascular beds is informative. Atherosclerosis is common in the normal hypoxemia pulmonary circulation, especially at ages >40 years.[13] When left-to-right shunts increase oxygen saturation in the pulmonary circulation, the prevalence of atherosclerosis remains the same or increases slightly.[13] There is no relation between atherosclerosis in the hypoxemic pulmonary circulation and in the normoxemic systemic circulation, except in the presence of hypercholesterolemia.[13]

Erythrocytosis: Hypocholesterolemia has been reported with polycythemia rubra vera (acyanotic nonhypoxemic erythrocytosis).[10] Hemoglobin and cholesterol levels increase after splenectomy for hereditary spherocytosis; a correlation has also been reported in healthy nonanemic subjects,[11] and a significant correlation was found in our patients in group B (Table 4). However, other studies that included myeloproliferative disorders found no correlation between hematocrit and total cholesterol,[10] and in our patients in groups A, C, and D, no correlation existed between hematocrit and total cholesterol (Table 4).

Genetic influences: Hypocholesterolemia tends to persist after cyanosis, hypoxemia, and erythrocytosis are eliminated by surgery (Figure 1). The persistence of hypocholesterolemia implies the induction or suppression of gene(s) that reduce cholesterol levels. Once the gene(s) are expressed, their effects may persist despite the elimination of the initiating stimulus. The clustering of hypocholesterolemia with specific congenital cardiac defects (Eisenmenger's syndrome atrial septal defect vs ventricular septal defect) suggests a genetic linkage. The lack of a relation between cholesterol level and age at repair and the failure of cholesterol levels to normalize decades after the surgical elimination of hypoxemia and erythrocytosis suggest a developmental genetic program that maintains childhood cholesterol levels and profiles and does not permit the emergence of adult lipoprotein characteristics. Changes in cholesterol ester transfer between lipoprotein particles caused by an excess of red cell membranes in erythrocytosis might explain changes in lipoprotein size and composition identified on chromatography and nuclear magnetic resonance spectroscopy, but would not explain the failure of lipoproteins to normalize after the surgical elimination of hypoxemia and erythrocytosis and would not explain the lack of a relation between hematocrit and cholesterol levels. High flow or high pressure may damage pulmonary endothelium and lead to changes in lipoprotein lipase, with a change in the conversion of VLDL to IDL or IDL to LDL, resulting in the larger LDL and IDL lipoprotein species found in gel filtration and nuclear magnetic resonance spectroscopy.

Hypoxemia is associated with a reduction in oxidized plasma LDL and a reduction in atherogenic intimal oxidized LDL. Larger LDL particles are relatively resistant to oxidation, and a lack of small, dense, oxidation-sensitive LDL may behave similarly.

Three variables may account for the low incidence of coronary atherosclerosis in CCHD in addition to hypocholesterolemia, namely, the upregulation of nitric oxide, hyperbilirubinemia, and low platelet counts.

Nitric oxide: The molecule is antiatherogenic, because it opposes platelet adherence and aggregation, stimulates the disaggregation of preformed platelet aggregates, inhibits monocyte adherence and infiltration, and turns off the transcription of intercellular adhesion molecule-1, which governs the endothelial adhesion of monocytes and inhibits smooth muscle proliferation.[14] Nitric oxide bioavailability is increased in CCHD because increased endothelial shear stress of erythrocytosis is a major factor in nitric oxide elaboration and eNOS gene expression.[14–16] In addition, red blood cells are nitric oxide reservoirs, and red cell mass is increased.[17,18]

Hyperbilirubinemia: Bilirubin is formed from the breakdown of heme, a process that is excessive in CCHD, because an increase in red cell mass coincides with an increase in unconjugated bilirubin, which is an endogenous antioxidant that inhibits LDL oxidation and reduces atherosclerotic risk.[19] Gilbert's syndrome, a benign disorder of hepatic bilirubin metabolism, is accompanied by elevated levels of unconjugated bilirubin and a reported immunity from coronary atherosclerosis.[19]

Low platelet counts: Platelet counts are typically low normal or thrombocytopenic in CCHD,[20] and low platelet

counts are antiatherogenic. About 1/4 of patients with CCHD have platelet counts of $<100 \times 10^9$/L.[21] Megakaryocytes delivered into the systemic arterial circulation by right-to-left shunts cannot shed platelets by cytoplasmic fragmentation in the pulmonary circulation, thus accounting for the low platelet counts.[20] Platelet counts correlate negatively and with the magnitude of the right-to-left shunt and with the hematocrit.[22]

Hereditary swine von Willebrand's disease is an atheroma-free model in which the largest multimers are preserved.[23] CCHD is characterized by a secondary form of von Willebrand's disease that is not antiatherogenic because the largest multimers are few or absent.[23] Uric acid has been implicated as an atherosclerotic risk factor,[24] but whether this applies to the secondary hyperuricemia in CCHD[25] is unknown. No effect was detected in our inherently cyanotic patients.

The normal dimensions of extramural coronary arteries have seldom been studied in vivo and are therefore uncertain.[26–28] Accordingly, our angiographic judgments between normal and mildly dilated vessels were imprecise, but when dilation and tortuosity were moderate, marked, or aneurysmal, grading was not in doubt.[28] Coronary arteries in CCHD are believed to enlarge initially because of endothelial vasodilator substances elaborated in response to increased endothelial shear stress of the viscous erythrocytotic perfusate.[15] However, dilation often exceeds the anticipated response to endothelial vasodilators per se (Figure 5). In our cyanotic patients who came to necropsy, ectatic coronary arteries were characterized microscopically by the loss of medial smooth muscle and increased collagen,[29] similar to "dilated coronopathy," which has been attributed to the loss of medial smooth muscle and an increase in collagen.[30]

Our data on fasting total cholesterol and fasting LDL and HDL cholesterol were incomplete because approximately 80% of our computer-stored chemistry panels were nonfasting. However, the prevalence of hypocholesterolemia might have been even greater if the specimens had been fasting. We depended chiefly on angiography, which cannot detect nonraised atherosclerotic plaques, a shortcoming compounded in the dilated coronary arteries of CCHD. It is noteworthy, however, that hypoxemic erythrocytotic residents of high altitudes are devoid of coronary atherosclerosis at necropsy.[2]

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