

## The coronary circulation in cyanotic congenital heart disease

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### Abstract

**Background:** Dilated coronary arteries, coronary blood flow, and the paucity of coronary atherosclerosis have not been studied in cyanotic congenital heart disease.

**Methods:** Coronary arteriograms were interpreted in 59 cyanotic adults, and dilated coronaries were examined histologically in 6. Coronary blood flow was determined with N-13 ammonia positron emission tomography in 14 Eisenmenger syndrome patients and in 10 controls. Total non-fasting cholesterols were retrieved in 279 patients who were divided into: Group A—143 cyanotic unoperated, Group B—47 acyanotic after operation, Group C—41 acyanotic unoperated, Group D—48 acyanotic before and after operation. Total cholesterol was <160 mg/ml in 58% of Group A and 51% of Group B. Low- (LDL) and high-density cholesterol (HDL) and triglycerides were determined in 57/82 hypocholesterolemic patients. Platelet counts were determined in 105 patients. Platelet production, megakaryocyte production, platelet destruction, and platelet activation were studied.

**Results:** Angiography—88% of extramural coronary arteries were mildly or moderately dilated to ectatic and tortuous. Loss of medial smooth muscle, increased medial collagen, and duplication of internal elastic lamina were identified histologically. Basal coronary flow was increased, but hyperemic flow following IV dipyridamole was comparable in patients and controls. Atherosclerosis was not detected in either the arteriograms or the necropsy specimens. Thrombocytopenic resulted from reduced platelet production.

**Conclusions:** Coronary arteries in cyanotic congenital heart disease dilate in response to endothelial vasodilators coupled with mural attenuation caused by medial abnormalities. Basal flow was increased, but flow reserve was normal. Coronary arteries were atheroma-free. © 2004 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Cyanotic congenital heart disease; Coronary circulation

This report comprises four separate but related studies of the coronary circulation in adults with cyanotic congenital heart disease, namely, pathogenesis of extramural coronary artery dilatation, basal coronary blood flow and coronary flow reserve, relative immunity from atherosclerosis, and pathogenesis of low platelet counts. The protocol for each study was approved by the UCLA Institutional Review Board.

In 1966, the term “coronary artery ectasia” was applied to the dilated tortuous extramural coronary arteries of a 24-year-old man with cyanotic Fallot’s tetralogy [1]. Two years later, striking dilatation and tortuosity of extramural coronary arteries were described at angiography and necropsy in a 38-year-old cyanotic woman with the

Taussig Bing anomaly [2]. In 1971, Arias-Stella and Topilsky [3] reported dilatation and tortuosity of extramural coronary arteries in hypoxemic erythrocytotic residents of high altitude. Subsequent studies on conduit arteries disclosed a direct relationship between perfusate viscosity and arterial diameter, indicating that increased shear stress at the luminal surface provoked elaboration of endothelial vasodilator substances [4]. In cyanotic congenital heart disease, extramural coronaries dilate in response to nitric oxide and prostaglandins elaborated in response to endothelial shear stress induced by the viscous erythrocytotic perfusate [5], but dilatation often exceeds the anticipated vasodilator response per se. It was hypothesized that the excessive dilatation might result from endothelial-related vasodilators acting in concert with mural attenuation caused by medial abnormalities [6], analogous to the medial abnormalities that attenuate great arterial walls in many types of congenital

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heart disease, causing dilatation out of proportion to developmental and hemodynamic expectations [7]. It was then hypothesized that the dilated extramural coronary arteries should carry increased basal flow that might encroach upon coronary flow reserve, rendering the myocardium vulnerable to stress-induced ischemia [8]. The next hypothesis was derived from observations on hypoxic erythrocytotic residents of high altitude in whom clinical and necropsy evidence of coronary atherosclerosis was virtually nil, and in whom total cholesterol and LDL cholesterol levels were low and HDL levels were elevated [9]. The final hypothesis focused on the pathogenesis of low platelet counts and thrombocytopenia which are antiatherogenic and are prevalent in adults with CCHD [10].

## 1. Study 1. Dilatation and tortuosity of extramural coronary arteries [6]

### 1.1. Materials and methods

#### 1.1.1. Coronary angiography

Coronary arteriograms were reinterpreted in 70 adults with cyanotic congenital heart disease without knowledge of the original angiographic interpretations with which the blinded reinterpretations were compared. Thirty-three patients were female aged 23 to 54 years (mean  $41 \pm 5$ ) and 25 were male aged 18 to 56 years (mean  $36 \pm 4$ ).

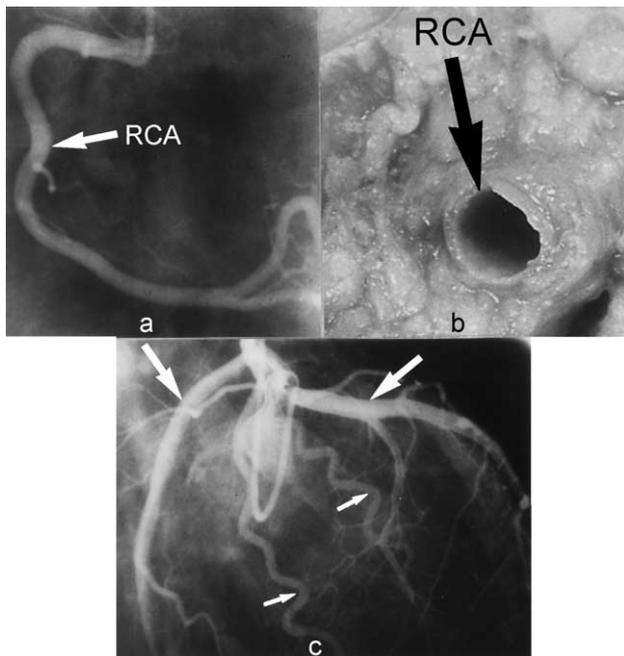


Fig. 1. (a,c) Coronary arteriograms showing a dilated atheroma-free right coronary artery and dilated, tortuous atheroma-free left coronary arteries in a 45 year old man with an Eisenmenger ventricular septal defect. (b) Cross section of a dilated atheroma-free right coronary artery in a 36 year old man with an Eisenmenger ventricular septal defect.

Coronary visualization was of high quality in 59/70 cases, including all 30 selective arteriograms and 29/40 aortic root angiograms. Coronary artery size (dilatation) was based on catheter diameter and was compared to normal coronary artery diameters [11–13]. Grid-based calibration was avoided because of magnification error. The coronary arteries were graded as normal to mildly dilated, mildly dilated but tortuous, moderately dilated and tortuous, and ectatic and tortuous (Fig. 1).

#### 1.1.2. Gross morphology and histopathology

Necropsy specimens of dilated extramural coronary arteries (Fig. 2) from six adults with cyanotic congenital heart disease were sectioned along their epicardial course at proximal, mid and distal sites, and examined histologically with hematoxylin/eosin, trichome, and alcian blue stains (Fig. 3).

### 1.2. Results

The extramural coronary arteries were mildly dilated and tortuous to ectatic/tortuous in 88% of the arteriograms (Fig. 1). Histology of the dilated coronary arteries was characterized by loss of medial smooth muscle, increased medial collagen, fragmentation of the internal elastic lamina, and fibrointimal hyperplasia (Fig. 3).

## 2. Study 2. Myocardial perfusion and perfusion reserve [8]

### 2.1. Materials and methods

Seven males and seven females with Eisenmenger syndrome, aged 20 to 43 years (mean  $34.1 \pm 6.5$ ), were studied with positron emission tomography. All patients had biventricular hearts that provided three regions of interest—right ventricular free wall, left ventricular free wall, and ventricular septum. Diagnoses were established by transthoracic echocardiography. Mean hematocrits were  $62.2 \pm 4.8$ , and all were iron replete. Ten age- and sex-matched normal volunteers served as controls (Table 1).

N-13 ammonia perfusion images were obtained in patients and controls with a CTI-Siemens tomograph at baseline and following stress induced by intravenous dipyridamole. Regions of interest were placed in short axis images on the right ventricle, left ventricle and ventricular septum at apical, mid ventricular and basal levels. Maximal hyperemic blood flow was divided by basal coronary blood flow to obtain coronary flow reserve.

### 2.2. Results

Basal perfusion in patients was comparable in each region of interest and was higher than in controls. Hyperemic



Fig. 2. Striking gross appearance of an ectatic, tortuous left anterior descending coronary artery in a 45 year old woman with an Eisenmenger ventricular septal defect.

measurements in patients were comparable to controls and disclosed normal coronary flow reserve (Fig. 4).

### 3. Study 3. The paucity of coronary atherosclerosis [9]

#### 3.1. Materials and methods

Two hundred seventy nine patients were divided into four groups (Fig. 5): *Group A*—143 cyanotic unoperated patients, 54 male and 89 female aged 18 to 69 years (mean  $36 \pm 11$ ), mean iron replete hematocrit  $61\% \pm 8$ , mean systemic arterial oxygen saturation  $78 \pm 3$ ; *Group B*—47 cyanotic patients who were rendered acyanotic by operation at ages 22 to 69 years, mean postoperative follow-up 16.9 years, mean postoperative hematocrit  $41\% \pm 5$ ; *Group C*—

Table 1

Causes of cyanotic congenital heart disease

(1) Natural connections
(a) Isolated intracardiac communications with or without pulmonary outflow tract obstruction (Eisenmenger syndrome)
• Ventricular septal defect
• Atrial septal defect
(b) Complex lesions with or without pulmonary outflow tract obstruction (Eisenmenger physiology)
• Atrioventricular septal defect
• Ventriculo-arterial discordance (dextro-transposition of the great arteries) or atrioventricular and ventriculo-arterial discordance (levo-transposition of the great arteries) with a restrictive or nonrestrictive ventricular septal defect
• Tetralogy of Fallot (unoperated)
• Various forms of truncus arteriosus
• Tricuspid atresia
• Various forms of double inleft ventricles
• Ebstein anomaly with atrial septal defect
(c) Large extracardiac communications (aorto-pulmonary connections)
• Patent ductus arteriosus
• Aortopulmonary window
• Aortopulmonary collaterals in patients with pulmonary atresia
(2) Palliative (unnatural) connections to augment restricted pulmonary blood flow
• Waterston anastomosis (ascending aorta to right pulmonary artery)
• Potts anastomosis (descending aorta to left pulmonary artery)
• Blalock Taussig anastomosis (subclavian artery to ipsilateral pulmonary artery)

41 acyanotic unoperated patients, 22 male and 19 female aged 22 to 75 years (mean  $44 \pm 15$ ), mean hematocrit  $41 \pm 5$ ; *Group D*—48 patients who were acyanotic both before and after operation, 24 female and 24 male age 21 to 70 (mean  $42 \pm 4$ ), mean post operative follow-up 15 years, mean hematocrit  $42 \pm 3$ . No patient had a myeloproliferative disease, none was malnourished, none had ever taken a cholesterol-lowering medication, and all were born and lived at sea level (Table 2).

#### 3.2. Coronary arteriograms

Fifty-nine Group A patients, 25 females aged 38 to 54 years (mean  $43 \pm 4$ ) and 24 males aged 36 to 56 years (mean  $41 \pm 6$ ) had high quality coronary arteriograms that were

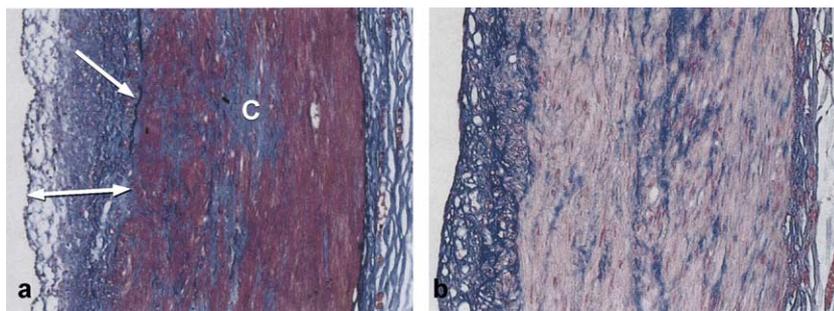


Fig. 3. Histologic appearance of the ectatic coronary artery shown in Fig. 2. (a) Trichrome stain showing disruption of the internal elastic lamina (left upper arrow), increased medial collagen (C) that stains blue, and fibrointimal hyperplasia (paired arrows). (b) Alcian blue stain showing increased extracellular matrix (blue) scattered throughout the media. Medial smooth muscle cells are pink. There was no atherosclerosis.

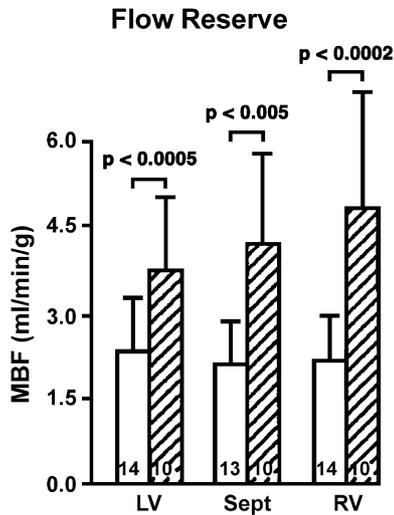


Fig. 4. Flow reserve in patients (white bars) was preserved in the LV (left ventricle), Sept (ventricular septum), and RV (right ventricle) following pharmacologic stress with intravenous dipyridamole. Cross-hatched bars represent controls.

reinterpreted without knowledge of the original angiographic interpretations with which the blinded reinterpretations were compared.

3.3. Gross morphology and histopathology

Gross (Fig. 2) and histologic examination (Fig. 3) of the dilated extramural coronary arteries were obtained in six necropsy patients (see Study 1).

3.4. Serum cholesterol levels

Non-fasting total cholesterol values were retrieved from computer-stored chemistry panels (Fig. 5). Total cholesterol

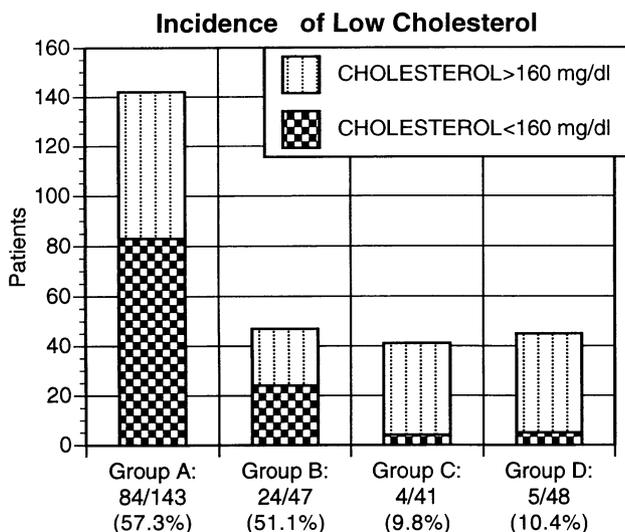


Fig. 5. Incidence of low total cholesterol levels (<160 mg/dl) in Study Groups A, B, C and D.

Table 2

Stage of iron deficiency and laboratory findings

	Iron store depletion	Iron-deficient erythropoiesis	Iron-deficiency anemia
Hemoglobin	normal	Normal to ↓	↓↓
Mean corpuscular volume	normal	Normal	↓↓
Erythrocyte protoporphyrin	normal	↑	↑↑
Serum iron	normal	↓↓	↓↓↓
Total iron-binding capacity	normal	↑	↑↑
Serum ferritin	↓	↓↓	↓↓

From Ref. [9].

<160 mg/dl was considered low because that level represented the 10th percentile in the Framingham Study (Fig. 6) [14]. Low-density cholesterol (LDL), high-density cholesterol (HDL) and triglycerides were determined in 57/82 of the hypocholesterolemic patients, and fasting lipoprotein levels were determined in 20/82 patients.

3.5. Results

In the 59 coronary arteriograms (Fig. 1) and in the 6 necropsy specimens (Figs. 1 and 3), evidence of atherosclerosis was minimal to absent. The gross morphology and histopathology were described in Study 1. Groups A and B (inherently cyanotic patients and cyanotic patients who were rendered acyanotic by operation) had significantly lower total cholesterol levels than acyanotic unoperated Group C or acyanotic operated Group D patients (Figs. 5 and 6). No significant difference in mean total cholesterol levels was found between males and females in any group. Groups A and B had reductions in all cholesterol fractions compared to Groups C and D. There was no significant correlation between hematocrit levels and total cholesterol levels in Groups A, C and D, but there was a significant correlation for Group B.

4. Study 4. Low platelet counts and thrombocytopenia [10]

4.1. Materials and methods

One hundred and five cyanotic patients, 60 male and 45 female, aged 21 to 54 years (mean 41±5), were studied. Electronic platelet counts were supplemented flow cytometry counts. Platelet production was assessed by quantification of reticulated platelets employing fluochromes and flow cytometry. Megakaryocyte production (mass) was assessed indirectly by thrombopoietin levels using a quantitative sandwich enzyme immunoassay technique. Platelet production was based on prothrombin time, activated partial thromboplastin time and D-dimers. Platelet activation was determined by

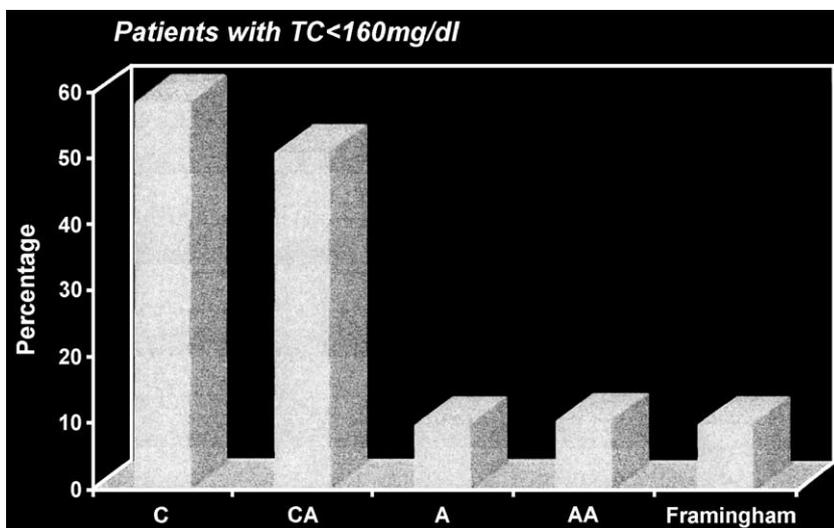


Fig. 6. Percentage of patients with total cholesterol levels (TC) <160 mg/dl in Study Groups A, B, C and D. Fifty-eight percent of cyanotic unoperated patients (C) had total non-fasting cholesterol levels <160 mg/dl. Fifty-one percent of initially cyanotic hypocholesterolemic patients had total cholesterol levels <160 mg/dl after being rendered acyanotic by operation (CA). Unoperated acyanotic patients (A) and patients who were acyanotic both before and after operation (AA) had the same prevalence of total cholesterol levels <160 mg/dl as the Framingham controls.

platelet factor 4 and  $\beta$  thromboglobulin. Reference ranges were derived from 20 normal controls to avoid the effect of turbulent flow and increased endothelial shear stress on platelet surfaces of certain acyanotic congenital heart disease patients.

#### 4.2. Results

In 24% of patients (25/105), platelet counts were  $<100 \times 10^9/l$  (mean  $68.2 \pm 6$ ). In the remaining 80 patients, platelet counts averaged  $110 \pm 10^9/l$ ; 21 of the 25

thrombocytopenic patients had Eisenmenger syndrome, 3 had Fallot's tetralogy, and 1 had complete transposition of the great arteries with pulmonary stenosis and ventricular septal defect. All 25 thrombocytopenic patients had a significant decrease in the absolute number of reticulated platelets signifying a reduction in platelet production. Platelet counts were inversely proportional to hematocrit levels (Fig. 7). Megakaryocyte production (mass) was normal or only slightly reduced based on normal thrombopoietin levels. Platelet activation was absent or minimal as indicated by near normal platelet factor 4 and  $\beta$  thromboglobulin.

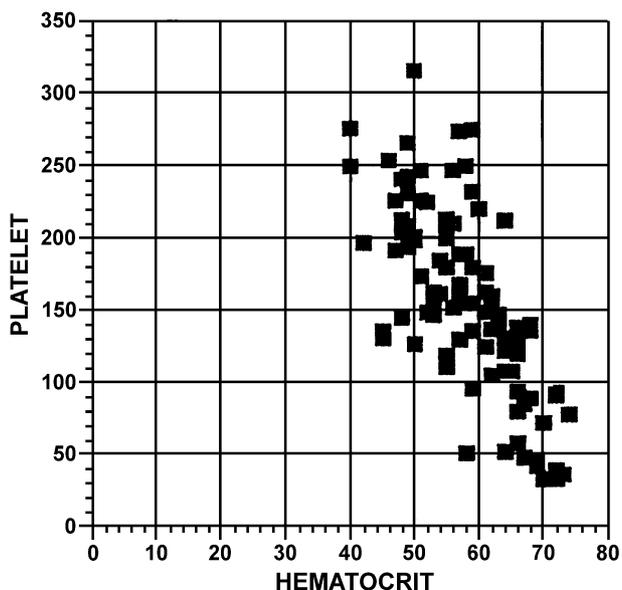


Fig. 7. Platelet counts were inversely proportional to hematocrit levels in patients with cyanotic congenital heart disease.

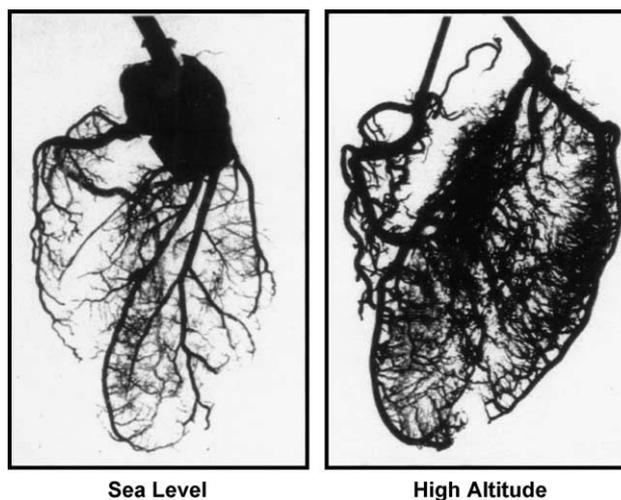


Fig. 8. Casts of the coronary vascular bed derived from acrylic resin injections in sea level residents and in age-matched acclimatized residents of high altitude. The casts from high altitude residents disclosed a much greater density of the coronary microcirculation. From Ref. [3].

**5. Discussion**

Mild to moderate dilatation of the extramural coronary arteries in cyanotic congenital heart disease (Fig. 1a,c), is in response to endothelial vasodilator nitric oxide and prostaglandins, the elaboration of which is provoked by increased endothelial shear stress of the viscous erythrocytotic perfusate. However, the striking dilatation represented by coronary ectasia (Fig. 2) cannot be ascribed to endothelial vasodilator substances per se, but is due to medial structural abnormalities (Fig. 2b) that attenuate the coronary arterial walls and act in concert with vasodilatation. “Dilated coronopathy” reported in 3% of routine coronary arteriograms refers to mural attenuation caused by loss of medial smooth muscle and an increase in collagen [15]. Marfan syndrome is associated with abnormalities of the extramural coronary arteries that principally involve the media but also include the internal elastic lamina [16].

Because the chronically dilated extramural coronary arteries in cyanotic congenital heart disease have a limited

capacity to dilate further, and because myocardial oxygen extraction is inherently maximal, the potential oxygen debt incurred by systemic arterial hypoxemia may be inadequately met. Basal coronary flow as determined by N-13 ammonia positron emission tomography was increased to the same degree in the right ventricular and left ventricular free walls and in the ventricular septum, but hyperemic perfusion, coronary vascular resistance and flow reserve were normal in each of the three regions of interest (Fig. 4). Although these studies were not designed to determine the mechanism(s) by which flow reserve is preserved in the face of increased basal coronary flow, the results imply remodeling of the intramyocardial coronary microcirculation, perhaps vasculogenesis in response to hypoxemic stimulation induced by vascular endothelial growth factor from myocardial smooth muscle cells and upregulation of vascular endothelial growth factor receptor-1 in heart endothelial cells [17]. In addition, nitric oxide is upregulated in cyanotic congenital heart disease and, as a mediator of angiogenesis [18], may contribute to remodeling of the coronary microcirculation. Interestingly, hypoxemic resi-

Table 3  
Clinical assessment of patients with cyanotic congenital heart disease

Name: ..... Date of Birth: ...../...../19..... Clinical Visit: ...../...../2003

Presence and Severity of Hyperviscosity Symptoms (Secondary Erythrocytosis!)					
0 Absent	Does not bother	2 Moderate	Interferes with some but not most activities		
1 Mild	Bothers without interfering with normal activities	3 Severe	Interferes with most or all activities		

	Hyperviscosity Symptoms	Absent 0	Mild 1	Moderate 2	Severe 3
Erythrocytosis	Headache				
	Faintness, dizziness, lightheadedness				
	Slow mentation, impaired alertness, irritability, a sense of distance or dissociation				
	Visual disturbances (blurred or double vision), scotoma				
	Paresthesias of fingers, toes, or lips				
	Tinnitus				
	Fatigue, lassitude, lethargy				
	Myalgias muscle weakness, anorexia				
	Restless legs				
Bleeding and Ischemic Events					
Hemorrhagic Diathesis (not requiring medical attention)	Easy bruising (fragile skin)				
	Gingival bleeding (fragile gums)				
	Hemoptysis				
	Epistaxis				
	Menorrhagia (menstruation lasting more than 7 days)				
		No		Yes (specify)	
Major Bleeding (requiring medical attention)	Hemoptysis				
	Traumatic bleeding (accidental injury, surgery)				
	Others				
Ischemic Events	Stroke / Transient Ischemic Attack (TIA)				
	Others				

Phlebotomy since last visit?       Yes (.....)    No      Iron supplements or vitamins containing iron ?       Yes       No

Aspirin?       Yes       No      Anticoagulants?       Yes (specify:.....)       No

Annual Flu Shot?       Yes       No      Pneumovax?       Yes (Date: ..... )       No

Modified from Refs. [1,2,19].

dents acclimatized to high altitude have a striking increase in the number of secondary arterial branches leaving the main coronary arteries and in the number of peripheral ramifications [3] (Fig. 8). Hypoxemia in cyanotic congenital heart disease might excite similar remodeling of the coronary microcirculation.

Five coexisting but independent variables contribute to the low incidence of coronary atherosclerosis in cyanotic congenital heart disease—hypocholesterolemia (Study 3), hypoxemia, upregulation of nitric oxide, hyperbilirubinemia, and low platelet counts (Study 4).

Although high altitude is a scarcely recognized cause of hypocholesterolemia, hypoxemic erythrocytotic residents acclimatized to high altitude have reduced levels of total cholesterol and LDL cholesterol, elevated levels of HDL cholesterol, and are virtually devoid of clinical and necropsy evidence of coronary atherosclerosis [3,19]. Cyanotic congenital heart disease is a previously unrecognized cause of hypocholesterolemia, the etiology of which includes cyanosis (systemic arterial hypoxemia), erythrocytosis, and genetic factors. Hypoxemia and erythrocytosis, which need not be present at birth, are obligatory albeit insufficient causes, and the relationship between hypoxemia, erythrocytosis and hypocholesterolemia are unclear. Intrauterine hypoxemia does not influence fetal cholesterol levels [20], and in myeloproliferative diseases [21] and in cyanotic congenital heart disease, there is no correlation between cholesterol levels and red cell mass. Persistence of hypocholesterolemia after surgical elimination of cyanosis, hypoxemia and erythrocytosis implies induction or suppression of gene(s) that induce hypocholesterolemia, and also imply that once the gene(s) are expressed, their effects tend to persist despite elimination of the initiating stimulus (Table 3).

Atherogenic oxidized LDL cholesterol is reduced in cyanotic congenital heart disease because hypoxemia is associated with reduced oxidized plasma LDL and reduced intimal oxidized LDL. Larger LDL particles are relatively resistant to oxidation, and the lack of small dense oxidation-sensitive LDL may act in a similar fashion [22].

Nitric oxide is antiatherogenic because it opposes platelet adherence and aggregation, stimulates disaggregation of preformed platelet aggregates, inhibits monocyte adherence and infiltration, and turns off transcription of ICAM 1 that governs smooth muscle proliferation and endothelial adhesion of monocytes [23]. Nitric oxide bioavailability is increased in cyanotic congenital heart disease because erythrocytosis is a major factor in nitric oxide elaboration and eNOS gene expression [23], and because red blood cells are nitric oxide reservoirs [18,24].

Gilbert's disease, a benign hereditary disorder of hepatic bilirubin metabolism, is accompanied by elevated levels of unconjugated bilirubin and immunity from coronary atherosclerosis [25]. In cyanotic congenital heart disease, the breakdown of heme is excessive because of the increase in red cell mass, and coincides with an

Table 4

## Risk reduction strategies

- Avoidance of inappropriate (prophylactic) phlebotomies
- Avoidance and treatment of anemia (caveat: cyanotic patients require a higher hemoglobin level than healthy adults!)
- Avoidance of iron deficiency
- Avoidance of dehydration
- Avoidance of anti-inflammatory drugs/routine oral anticoagulation
- Avoidance of smoking
- Avoidance of air embolism (paradoxical air embolism) by the use of an air filter in case of an intravenous line
- Avoidance of infectious diseases (annual flu shot, pneumovax vaccination)

increase in unconjugated bilirubin which is an endogenous antioxidant.

Low platelet counts are antiatherogenic [26], and in cyanotic congenital heart disease platelet, platelet counts are typically low normal or thrombocytopenic because shunted systemic venous megakaryocytes bypass the pulmonary vascular bed where platelets are shed by cytoplasmic fragmentation [27]. It is therefore not surprising that thrombocytopenia (Study 4) is caused by decreased platelet production in face of normal megakaryocyte mass, a conclusion based on a significant reduction in the absolute number of reticulated platelets. The negative correlation between platelet counts, hematocrit and the magnitude of right-to-left shunts [28] (Fig. 7) is in accord with these observations (Table 4).

## 6. Conclusions

In cyanotic congenital heart disease, the extramural coronary arteries initially dilate in response to endothelial vasodilator substances, and then dilate further because of mural attenuation caused by coexisting medial abnormalities. Basal coronary blood flow is increased in the dilated extramural coronary arteries, but the increase in basal flow does not encroach upon flow reserve because the coronary microcirculation apparently remodels in response to vascular endothelial growth factor and nitric oxide. The dilated extramural coronary arteries are atheroma-free because of the combined antiatherogenic effects of hypocholesterolemia, hypoxemia, upregulation of nitric oxide, hyperbilirubinemia, and low platelet counts.

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