Cardiovascular Medicine
Congenital Heart Disease: Cyanotic Disorders

From ACP Medicine Online
Posted 06/07/2006

Larry T. Mahoney, MD; David J. Skorton, MD

Definition and Mechanisms
Central cyanosis is caused by an intracardiac shunt or an intrapulmonary right-to-left shunt. Cyanosis becomes evident when reduced (deoxygenated) capillary hemoglobin reaches about 5 g/dl, although this depends on the total hemoglobin concentration: cyanosis is more readily apparent in a patient with polycythemia and is less apparent in a patient with anemia. Mild cyanosis is difficult to detect. Generally, cyanosis does not become clinically apparent until the oxygen saturation falls below 85% (assuming a normal hemoglobin level). Patients with long-standing arterial desaturation will develop clubbing of the fingernails and toenails. Clubbing is characterized by thickening and widening of the nailbeds and loss of the angle between the nail and nail bed, producing a convex nail.

It is helpful to categorize cyanotic CHDs in terms of their effect on pulmonary blood flow. Defects producing decreased pulmonary blood flow include tetralogy of Fallot, tricuspid atresia, Ebstein anomaly, and pulmonary atresia. Defects associated with increased pulmonary blood flow include persistent truncus arteriosus, transposition of the great arteries with or without VSD or PDA, total anomalous venous return, a single or common ventricle, and hypoplastic left heart syndrome. Acyanotic patients with large left-to-right shunts may develop pulmonary vascular occlusive disease (Eisenmenger syndrome).

Adult patients with cyanotic CHD are at increased risk for hyperviscosity secondary to erythrocytosis. The erythrocytosis develops as a compensatory mechanism for red cell oxygen desaturation: a significantly increased red cell mass is necessary to deliver an adequate volume of oxygen to peripheral tissues, given the sometimes severe degree of desaturation. Venous and arterial thrombosis with secondary cerebrovascular accidents have been well documented in cyanotic CHD and have been attributed both to the increased red blood cell mass and to associated iron deficiency anemia, which also increases blood viscosity. This risk is increased in the presence of hypertension or atrial fibrillation and in patients with a history of phlebotomy and microcytosis, suggesting the need for a more conservative approach to phlebotomy and aggressive treatment of iron deficiency.

Eisenmenger Syndrome
A serious complication of long-standing left-to-right shunts in the atria, ventricles, or great arteries is the development of severe, irreversible pulmonary hypertension, which is termed Eisenmenger syndrome.

Pathophysiology
Normally, the pulmonary vascular resistance is substantially lower than systemic vascular resistance; thus, large intracardiac or great artery communications tend to produce left-to-right shunting. As pulmonary vascular resistance rises, resistance to flow into the pulmonary circulation will eventually exceed that into the systemic circulation, and right-to-left shunting will occur. This will result in varying degrees of cyanosis as well as other physical findings of pulmonary hypertension. Unlike patients with polycythemia vera or polycythemia from chronic obstructive pulmonary disease, patients with Eisenmenger syndrome will often require hematocrits in the 60s, or even low 70s, to deliver sufficient oxygen to tissues to avoid ischemic symptoms.
Clinical Presentation

Patients with Eisenmenger syndrome may be asymptomatic except for cyanosis. Eventually, many patients will note decreased exercise tolerance and chest discomfort, often reminiscent of angina pectoris. If secondary erythrocytosis reaches severe levels, patients may develop symptoms of hyperviscosity, including visual disturbances, headaches, and other complaints.

Physical examination of a patient with Eisenmenger syndrome will reveal manifestations of pulmonary hypertension, including a loud pulmonary component of the second heart sound and the high-pitched diastolic murmur of high-pressure pulmonary regurgitation (the Graham Steell murmur). Additional findings include cyanosis, clubbing, and RV lift or heave.

Laboratory Tests

Electrocardiography. The ECG shows right axis deviation and RVH, exhibited as tall R waves and ST-T abnormalities in V1 through V3.

Radiologic studies. The chest x-ray will show enlarged central pulmonary arteries with peripheral arterial pruning. Cardiomegaly with specific chamber enlargement will reflect the underlying defect. Right-sided cardiac catheterization often is needed to assess pulmonary arterial pressure and resistance.

Echocardiography. Echocardiography can identify and quantify the underlying cardiac shunt and provide an estimate of right heart pressures.

Management

Patients with Eisenmenger syndrome may live for decades after the diagnosis is made. Alternatively, sudden death from ventricular arrhythmias may occur. Because pulmonary resistance is high and fixed in these patients, care needs to be taken to avoid situations that may lead to sudden decreases in systemic vascular resistance, which would exacerbate the right-to-left shunting, sometimes in a life-threatening manner. This would include avoidance of overly hot environments and dehydration; in addition, care should be taken during anesthesia or when using vasodilator drugs. Pregnancy is another state in which systemic vascular resistance falls; thus, pregnancy is extremely dangerous for a mother with pulmonary hypertension, as well as for her fetus. Iron deficiency should be treated if present. Only rarely will phlebotomy be required to relieve symptoms of hyperviscosity. A relatively recent therapeutic option for Eisenmenger syndrome is the use of prostacyclin or endothelin-related drugs to lower pulmonary vascular resistance. Heart-lung or lung transplantation has been successfully performed in some patients with Eisenmenger syndrome.

Tetralogy of Fallot

Pathophysiology

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease. Classically, the syndrome includes pulmonary stenosis (subvalvar, valvar, supravalvar, or a combination of all of these), RVH, subaortic VSD, and dextropositioning of the aorta so that it overrides the interventricular septum. Associated anomalies include right aortic arch (25%), atrial septal defect (10%), and coronary artery anomalies (10%). Approximately 15% of patients with tetralogy of Fallot have a deletion of chromosome 22q11 (CATCH 22 syndrome: cardiac anomalies, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia, and 22q11 deletion).

Surgical Repair in Childhood

Current surgical practice warrants early repair, usually in the first year of life. Without surgery, survival beyond 20 years of age is uncommon.

Surgical repair consists of patch closure of the VSD and alleviation of the RV outflow tract obstruction by one or more of the following methods: infundibular muscle resection, pulmonary valvotomy, outflow tract or transannular patch augmentation, and patch augmentation of the main or proximal branch pulmonary arteries. In some cases, it is necessary to place a conduit from the RV to the pulmonary artery. The conduit may be valved or nonvalved, and it may be bioprosthetic or a homograft.

When pulmonary blood flow is inadequate, surgical repair includes a shunt from the systemic circulation to the pulmonary artery to provide additional pulmonary flow. This may consist of a Blalock-Taussig shunt, a Potts shunt, or a Waterston shunt. The classic Blalock-Taussig shunt connects the subclavian artery to the pulmonary artery; the modified form comprises an interposed tube graft, usually of expanded polytetrafluoroethylene [Gore-Tex]. A Potts shunt connects the descending aorta to the left pulmonary artery. A Waterston shunt connects the ascending aorta to the right pulmonary artery [see Figure 4 -- omitted].

Clinical Presentation after Repair
In patients who have undergone surgical repair of tetralogy of Fallot, the examination focuses on residual defects. Not uncommonly, these patients have murmur related to residual outflow tract obstruction and mild to severe pulmonary regurgitation (PR), which produces a to-and-fro murmur. The severity of RV outflow tract obstruction directly determines the presence and degree of cyanosis. Systolic ejection murmurs are inversely related to the severity of the obstruction: a short, soft murmur suggests severe obstruction with a large right-to-left ventricular level shunt and minimal forward flow in the pulmonary artery, whereas a long, harsh murmur suggests minimal obstruction.

Patent shunts will produce a continuous murmur. The degree of cyanosis will depend on the adequacy of pulmonary blood flow provided by the shunt.

A residual VSD may be detected. With increasing RV volume overload, the patient may experience exercise intolerance, right heart failure, and arrhythmias.

**Laboratory Data**

**Electrocardiography.** In patients who have undergone operative repair of tetralogy of Fallot, the ECG typically shows sinus rhythm, right axis deviation, and RVH; most of these patients also have right bundle branch block. Atrial and ventricular arrhythmias may be detected, especially on a 24-hour monitoring study.

**Radiologic studies.** The findings on chest x-ray vary with the surgical history. A right aortic arch may be noted. The pulmonary artery segment is concave because of the variable degree of pulmonary artery hypoplasia, and the RVH results in an upturned apex; together, these produce the classic finding of a boot-shaped heart. Surgical intervention may result in significant pulmonary regurgitation that eventually will lead to volume overload of the heart, producing cardiomegaly. Over time, patch augmentation of the outflow tract may become aneurysmal, which may be indicated by an enlarged pulmonary artery segment. Asymmetrical pulmonary blood flow suggests significant branch pulmonary artery obstruction and can be best quantitated by a pulmonary flow study. MRI with MRA is very useful to identify residual defects and assess ventricular function, especially in patients with poor acoustic windows and inadequate echocardiographic studies.

**Echocardiography.** Echocardiography will establish the presence and severity of any residual defects, including progressive enlargement of the RV secondary to pulmonary regurgitation, a residual VSD, and continuous flow in a palliative shunt. Doppler studies will demonstrate the magnitude of the residual outflow tract gradient. The ascending aorta often is enlarged.

**Management**

Patients who have undergone repair of tetralogy of Fallot must be regularly monitored for progression of residual defects, particularly those with pulmonary regurgitation and conduit obstruction. Branch pulmonary artery stenosis may be approached with balloon angioplasty and stent placement. Repeat surgery should be considered in patients with a significant residual VSD; in patients whose RV pressure is greater than two thirds the systemic pressure because of residual obstruction; in patients with RV enlargement secondary to severe pulmonary regurgitation (which may mandate placement of a bioprosthetic valve, especially if there is associated tricuspid regurgitation [TR]); and in those with reduced exercise tolerance. Reoperation in adults can be performed with low risk. Aortic valve or aortic root replacement is occasionally required because of progressive root dilatation and AR. Ventricular arrhythmias, which are detected in 40% to 50% of patients, have been associated with older age at primary repair, RV volume overload, and QRS prolongation. Marked widening of the QRS to more than 180 msec and LV dysfunction have been identified as risk factors for sudden cardiac death. In such cases, consideration should be given to prophylactic placement of an implantable cardiac defibrillator. Patients should be counseled to follow endocarditis prophylaxis during procedures that place them at risk.

**Dextrotransposition of the Great Arteries**

**Pathophysiology**

In the most common form of transposition of the great arteries (TGA), dextro-TGA (D-TGA), the aorta arises in an anterior position from the RV, and the pulmonary artery arises posteriorly from the LV. There is complete separation of the pulmonary and systemic circulations: systemic blood flow traverses the right heart and enters the aorta, whereas pulmonary blood flow traverses the left heart and enters the pulmonary artery. Most surviving patients have a patent ductus arteriosus and foramen ovale, permitting mixing of the two circulations. About one third have associated anomalies, including ASD and VSD. Left ventricular outflow tract obstruction is not uncommon. Unless intracardiac mixing is improved, survival beyond the first year is unusual.

**Surgical Repair in Childhood**

Initial treatment of D-TGA includes infusion of prostaglandin E to maintain patency of the ductus arteriosus and balloon septostomy (Rashkind procedure) to permit better mixing at the atrial level. Surgery initially consisted of redirecting the systemic venous return to the LV and the pulmonary venous return to the RV. These so-called atrial switch operations (Mustard or Senning procedures),
which used a baffle within the atria, restored physiologic circulation but required the RV to function as the systemic ventricle. The arterial switch operation has replaced the atrial switch operation, at least in patients who have normal function of both semilunar valves. In the arterial switch operation, the pulmonary artery and aorta are first transected above the semilunar valves and coronary arteries, and then they are switched. The aorta is connected to the neo-aortic valve (formerly the pulmonic valve) arising from the LV, and the pulmonary artery is connected to the neopulmonary valve (formerly the aortic valve) arising from the RV. The coronary arteries are relocated to the neoaorta.

Patients with D-TGA and a large VSD may undergo the Rastelli procedure. The pulmonary artery is divided and oversewn. Flow from the LV must pass through the septal defect and is directed by a baffle to the aortic valve. A conduit from the RV to the pulmonary artery allows egress from the ventricle to the pulmonary circulation.

Clinical Presentation after Repair

Physical findings relate to the presence of associated anomalies (i.e., murmurs of VSD, PS, or PDA). Similarly, the larger the septal defect, the less severe the cyanosis.

Laboratory Tests

Electrocardiography. The ECG in patients with the atrial switch shows right axis deviation and RVH. In patients with the arterial switch, the ECG may be normal, provided coronary blood flow is not compromised.

Radiologic studies. Patients who have had the atrial switch procedure generally have cardiomegaly from a dilated RV, and the pulmonary artery may show preferential flow to the right lung. Patients with the arterial switch repair are likely to have normal heart size.

Echocardiography. Echocardiography is used to assess associated residual defects: depressed RV function, progressive TR, left ventricular outflow tract obstruction, residual VSD, or coronary artery perfusion abnormalities.

Management

The long-term outlook after the atrial switch is quite good, with actuarial survival of 80% at 28 years and 76% of survivors having no symptoms. However, these patients must be monitored for progressive RV enlargement and TR leading to ventricular dysfunction. Although this complication occurs in only 3% of cases, such patients may require cardiac transplantation if medical therapy is ineffective. Atrial arrhythmias, including sick sinus syndrome, are common. The atrial baffle may cause either systemic or pulmonary venous obstruction, which is addressed either by reoperation or by balloon angioplasty and stent placement.

The long-term prognosis of patients with the arterial switch is less well known, but arrhythmias are thought to be less frequent and to occur secondary to imperfections in the operative procedure. Patients should undergo nuclear medicine studies or stress testing to monitor for inadequate coronary perfusion secondary to coronary artery reimplantation abnormalities. Stenosis of the pulmonary artery (the most common complication) or stenosis at aortic anastomosis sites may occur. Complications of the Rastelli procedure include subaortic obstruction (baffle or VSD obstruction), conduit stenosis (with or without regurgitation), baffle leak, and branch pulmonary artery stenosis. Significant residual defects require reoperation.

The Univentricular Heart

Pathophysiology

A functional single ventricle may result from hypoplastic left heart syndrome (aortic atresia, mitral atresia, or both), tricuspid atresia, pulmonary atresia with intact ventricular septum, or an unbalanced AVSD resulting in hypoplasia of either the RV or LV.

Surgical Repair in Childhood

The initial presentation of univentricular heart in childhood may include severe cyanosis associated with a marked decrease in pulmonary blood flow, mild cyanosis and heart failure associated with intracardiac admixture of circulations and excessive pulmonary blood flow, or nearly balanced systemic and pulmonary blood flows and mild cyanosis. Patients who survive to adulthood generally have undergone one or more palliative surgical procedures; these include the Norwood, Glenn, and Fontan procedures.

Norwood. The Norwood operation establishes a single outlet from the single ventricle by anastomosing the hypoplastic ascending aorta to the main pulmonary artery, producing a so-called neoaorta and connecting the distal pulmonary artery to a systemic shunt, usually a modified Blalock-Taussig shunt [see Figure 5, part a – omitted]. Often, an atrial septectomy is required to allow complete mixing at the atrial level.
Glenn. The bidirectional Glenn procedure involves anastomosis of the SVC to the pulmonary artery. It includes takedown of a previously placed shunt and repair of any branch pulmonary artery stenosis [see Figure 5, part b -- omitted]. The term bidirectional refers to the fact that the right pulmonary artery remains in continuity with the left pulmonary artery; this contrasts with the classic Glenn procedure, which involves anastomosis of the SVC to a right pulmonary artery that has been disconnected from the main and left pulmonary arteries. The bidirectional Glenn procedure is now done at 4 to 6 months of age.

Fontan. The Fontan procedure is the final palliative procedure, providing direct connection of flow from the SVC and inferior vena cava (IVC) to the pulmonary circuit. Initially, this was a one-stage procedure that involved attaching the RA to the pulmonary artery or RV outflow tract and was performed in patients older than 4 years. Current practice is to stage the anastomosis of SVC and IVC to the pulmonary circuit, with the final stage, total cavopulmonary artery anastomosis, occurring at 2 to 3 years of age. The IVC is connected to the pulmonary artery either by a lateral tunnel placed in the RA to direct blood from the IVC to the proximal SVC stump, which is then attached to the pulmonary artery [see Figure 5, part c -- omitted], or by an extracardiac conduit connecting the IVC to the pulmonary artery directly [see Figure 5, part d -- omitted]. With any of these routes of flow, a small communication (fenestration) may be made between the caval blood flow conduit and the functional left atrium. Pulmonary blood flow is achieved by passive venous return without assistance of a ventricular pumping chamber. Any mild alteration of pulmonary pressure or resistance will impair adequacy of pulmonary blood flow.

Clinical Presentation after Repair

Clinical features are variable. Some patients may be well palliated, with near-normal oxygen saturation, acceptable activity levels, and negligible findings on cardiac examination. Others will demonstrate progressive heart failure as the single ventricle (especially if it is an anatomic RV) succumbs to the increased pressure and volume overload secondary to progressive atrioventricular valve regurgitation and myocardial dysfunction. Both atrial and ventricular arrhythmias are common. The sluggish pulmonary blood flow may predispose to in situ thrombosis and pulmonary embolism, which in turn will impede pulmonary blood flow by raising pulmonary arterial pressure.

Laboratory Tests

Electrocardiography. ECG findings are quite variable and may include atrial or ventricular enlargement, axis deviation, conduction abnormalities, and arrhythmias.

Radiologic studies. The chest x-ray may show progressive cardiomegaly. Pulmonary vascular markings may be unequal, indicating stenosis of one or more pulmonary artery branches. MRI with MRA may show areas of branch pulmonary artery stenosis and progressive changes in chamber size and ventricular function.

Echocardiography. Echocardiographic studies are aimed at following the progression of atrioventricular valve regurgitation, ventricular enlargement, and dysfunction, as well as detecting so-called smoke or clots in the systemic venous-to-pulmonary artery circuit.

Management

After surgical correction, patients demonstrate significant limitations in exercise tolerance because they rely on passive pulmonary blood flow that does not increase maximally with exertion. Postoperative arrhythmias are common. Arrhythmias may need to be managed medically, because radiofrequency ablation techniques may be limited by access problems secondary to the extracardiac or lateral tunnel connections between the venous circulation and the pulmonary artery. The need for reoperation after the Fontan procedure is infrequent, with the most common indication being placement of a mechanical pacemaker. Protein-losing enteropathy (PLE) is a serious problem after the Fontan operation. Its cause is not known but probably relates to increased systemic venous and thoracic duct pressures. There may also be a local autoimmune or allergic component in the intestinal wall. PLE is characterized by peripheral edema, malabsorption, and a low serum protein level. Complications have become less frequent with staged surgery and provision of an atrial fenestration. Some older patients may benefit from conversion of classic Fontan to a total cavopulmonary artery anastomosis. Cardiac transplantation may be necessary for systemic ventricular failure or intractable PLE.17

Ebstein Anomaly of the Tricuspid Valve

Pathophysiology

This uncommon anomaly of the tricuspid valve consists of adherence of the posterior and septal leaflets to the myocardium—causing a downward displacement of the functional annulus toward the RV apex—and enlareng the anterior leaflet. The end result is atrialization of the RV with resultant TR. In patients who present early in life, Ebstein anomaly is often found in association with other defects, including ASD and PS. Accessory pathways and clinical evidence of preexcitation are not uncommon, and arrhythmias are the most common presenting features in adults. There is an association with maternal lithium administration.
**Clinical Presentation**

Ebstein anomaly can become clinically evident at any age; the natural history of this lesion ranges from death in early life to adult survival without surgery, depending on the degree of regurgitation and whether significant arrhythmias are present. Cyanosis may occur, in neonates or adults, secondary to right-to-left shunting at the atrial level. Adult patients may complain of fatigue, shortness of breath, palpitations, or syncope. On auscultation, a murmur of TR is apparent and is often associated with a gallop rhythm, multiple systolic ejection sounds, and a widely split second sound.

**Laboratory Tests**

**Electrocardiography.** ECG findings are quite variable. The PR interval may be normal; short, with preexcitation; or prolonged. The axis may be superior or rightward, with or without a right bundle branch block. There may be evidence of RA enlargement. Arrhythmias are detected in 43% of adolescents and adults.\(^ {22} \)

**Radiologic studies.** The chest x-ray may show cardiomegaly with RA enlargement. Cardiac catheterization is not necessary unless there is concern regarding coronary artery disease or need for electrophysiologic assessment and possible radiofrequency ablation.

**Echocardiography.** Echocardiography can confirm the diagnosis and the degree of the tricuspid valve displacement (which may vary from mild tethering of the septal leaflet to severe apical displacement) and characterize the severity of TR [see Figure 6 -- omitted]. The anterior leaflet is large and sail-like and may produce RV outflow obstruction. The atrial septum should be assessed for size of defect and magnitude of shunting.

**Management**

Surgery is recommended for patients with symptomatic heart failure and cardiomegaly, cyanosis, or arrhythmias; tricuspid valvuloplasty is preferred over valve replacement.\(^ {15} \) Surgery is not recommended for asymptomatic patients,\(^ {22} \) although some authors have advocated surgery if significant cardiomegaly is present, because this may be a better predictor of sudden death than functional status.\(^ {23} \)

Click here to subscribe or purchase the full chapter. Mahoney, Larry T; Skorton, David J, 1 Cardiovascular Medicine, XV Congenital Heart Disease, ACP Medicine Online, Dale DC; Federman DD, Eds. WebMD Inc., New York, 2000. http://www.acpmedicine.com/

**Disclaimer**

Figures, tables, references and sidebars are available in the subscription edition of ACP Medicine.

Larry T. Mahoney, MD, Professor of Pediatrics and Director of Pediatric Cardiology, University of Iowa College of Medicine

David J. Skorton, MD, University of Iowa College of Medicine

ACP Medicine Online. 2002; ©2002 WebMD Inc.