Cardiac Ischemia in Pediatric Patients

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KEYWORDS

• Congenital heart disease • Kawasaki disease
• Coronary artery anomaly • Coronary artery ostial stenosis

Children and teenagers are frequently brought to primary care physicians with complaints of chest pain. In the minds of the patients, their parents, and their physicians, thoughts of a cardiac event with an unpleasant outcome are often conjured up in such situations. If a child experiences chest pain while he or she is on the school grounds, the teachers and school officials may become alarmed, demanding an immediate medical consultation. There is prevailing fear of sudden death or cardiac disability among lay people as well as medical professionals. This fear of chest pain in a child is triggered by our vivid experience with an adult who suffered acute coronary syndrome or news reports of a high-profile case of sudden cardiac death in a young athlete. Atherosclerotic heart disease as a basis for myocardial ischemia in children is very rare. The great majority of chest pain experienced by children and teenagers are noncardiac in origin. Cardiac ischemia in children is usually not an isolated disease in an otherwise normally formed coronary artery, but is part of more complex congenital or acquired diseases. Myocardial infarction in a child is seldom manifested as classic pressure-like angina pectoris, but may take nonspecific symptoms such as unusual irritability, nausea and vomiting, abdominal pain, shocked state, syncope, seizure, or sudden unexpected cardiac arrest. Some patients may develop silent nonfatal infarction.[1] Although cardiac ischemia is not a frequent occurrence, it must be recognized as a serious, life-threatening event. Pediatricians must be aware of these conditions, and stand ready to take prompt and appropriate actions to avoid irreversible consequences. This article lists and characterizes major causes of cardiac ischemia in children, describes signs and symptoms of each, and provides therapeutic considerations.

DEFINITION AND BACKGROUND

The word ischemia is derived from two Greek roots: *ischō*, to keep back, plus *haima*, blood. Myocardial ischemia implies inadequate perfusion of the myocardium usually as a result of coronary artery obstruction anywhere along the course of the epicardial

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Pediatr Clin N Am 57 (2010) 1261–1280
doi:10.1016/j.pcl.2010.09.007 **pediatric.theclinics.com**
0031-3955/10/$ – see front matter

artery from the ostium in the aorta to the minute intramyocardial branches. Obstruction may be due to intrinsic narrowing of the vessel lumen due to thickening of the wall, presence of thrombus within its lumen, extrinsic compression of the vessel from a nearby structure, kinking or stretching of the artery itself, or abnormal vasoreactivity or spasm.

Typically, in a normal subject, there are two coronary arteries arising from the right- and left-facing sinuses of Valsalva. The right coronary artery (RCA) typically courses along the right atrioventricular groove adjacent to the tricuspid valve ring and reaches the posterior crux of the heart. It gives off branches sequentially to the sinus node, right atrium, right ventricle (RV), atrioventricular node, and posteroinferior wall of the left ventricle (LV) in a majority of patients (so-called right dominant pattern). The main trunk of left coronary artery (LCA) tunnels under the main pulmonary artery and, as it resurfaces, bifurcates into the left anterior descending artery (LAD) and the left circumflex artery (LCX). The LAD courses on the anterior surface of the LV along the attachment of the ventricular septum to the free wall, supplying blood to the LV anterior wall and about two-thirds of the ventricular septum. The LCX courses along the left atrioventricular groove just outside the mitral valve ring, and gives off a large branch to the lateral wall of the LV. In a minority of patients the LCX crosses the posterior crux of the heart and extends into the posterior descending artery (so-called left dominant coronary pattern).

Embryologically, primordial coronary vessels are formed by endothelial precursor cells migrating from the liver and form networks of channels along the differentiating epicardium of the heart tube. These primitive vessels penetrate into the myocardium. These ingrowing vessels merge, acquire smooth muscle coats, and transform themselves into arteries.[2] The main right and left arterial channels eventually connect to the aorta. In normal subjects, there are no well-developed connections (collateral arteries) linking the RCAs and LCAs. Intercoronary collaterals may develop rapidly, especially in young children, when one of the major arteries is blocked by disease process.

Coronary arteries provide oxygen and fuel (in the form of glucose and free fatty acid) to actively contracting myocardial cells. Because increased tension within the ventricular walls during systole impedes blood flow, most of the coronary blood flow occurs during diastole. Thus, the aortic diastolic pressure is an important determinant of coronary perfusion. Any pathologic condition that lowers the diastolic pressure, such as aortic insufficiency or presence of an abnormal run-off from the aorta (eg, patent ductus arteriosus or arterovenous fistula) tends to have a negative impact on coronary perfusion.

CLASSIFICATION

Coronary artery diseases which form the basis of myocardial ischemia in children may be classified in terms of cause. Major classes include (1) congenital anomalies of the coronary arteries, (2) coronary artery complications associated with congenital heart disease, (3) coronary artery sequelae of Kawasaki disease, and (4) myocardial ischemia associated with hypertrophic cardiomyopathy (**Box 1**).

CONGENITAL ANOMALIES OF THE CORONARY ARTERIES

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA) or Bland-White-Garland Syndrome

This particular anomaly is most likely come to the attention of a primary care physician in an infant between a few weeks to 12 months of age (**Fig. 1**). There are a few patients with this anomaly who remain symptom-free and survive until adulthood. The

Box 1
Classification of cardiac ischemia in children

- Congenital coronary artery anomalies
  - Anomalous origin of LCA from the pulmonary artery (ALCAPA; Bland-White-Garland syndrome)
  - Origin of a coronary artery from the wrong aortic sinus with its course between the aorta and the pulmonary artery
- Coronary artery complications associated with congenital heart disease
  - Coronary artery obstruction after arterial switch operation for D-transposition of the great arteries
  - Coronary artery complication after repair of tetralogy of Fallot
  - Coronary artery ostial stenosis associated with supravalvar aortic stenosis (Williams syndrome)
  - Coronary artery obstruction associated with pulmonary atresia with intact ventricular septum
- Coronary artery sequelae of Kawasaki disease
  - Thrombotic occlusion of large coronary artery aneurysm
  - Coronary artery stenosis at ends of large aneurysm
  - Obliterative coronary arteritis without large aneurysm (rare)
- Myocardial ischemia associated with hypertrophic cardiomyopathy
- Myocardial ischemia associated with cocaine use

prevalence of this anomaly is 1 in 300,000 live births. The predominant symptoms in infancy include pallor, sweatiness, rapid breathing, and episodes of extreme fussiness during feedings. Given early detection and prompt referral to a tertiary care facility, this rare congenital anomaly can be surgically corrected and the patient may survive with a good quality of life. Failure to diagnose this problem on a timely manner may result in early death due to congestive heart failure. Although this condition was known to pathologists as far back as the 19th century, its first rather graphic clinical description was published by Bland and colleagues[3] in 1933. The LCA originates from the main pulmonary artery, and follows the usual distribution and branching pattern. During the fetal life and immediate neonatal period, blood flows into the LCA in a normal forward direction owing to relatively high pulmonary artery diastolic pressure. However, after the postnatal drop in pulmonary vascular resistance, the RV can no longer generate high enough pressure to drive blood forward into the myocardium. Thus, myocardial ischemia ensues over the LCA territory. Myocardial ischemia, in turn, stimulates development of collateral arteries bridging between the RCA and the LCA. In a few exceptional patients, intercoronary collaterals develop rapidly and adequately, so that the LV myocardium remains viable. However, in a majority of patients, the LV will suffer severe ischemic damage.

Physical examination may show tachypnea, tachycardia, and pale cool and sweaty skin. One may hear distant heart tones and systolic murmur over the cardiac apex due to mitral regurgitation. The chest radiograph may show cardiomegaly with or without signs of passive pulmonary congestion. The ECG may suggest ischemic change or infarction pattern over the left anterior wall. Echocardiogram may show dilated poorly contracting LV with dyskinetic or akinetic anterolateral wall and ventricular septum. Careful color Doppler flow mapping may reveal flow in the LCA directed toward the

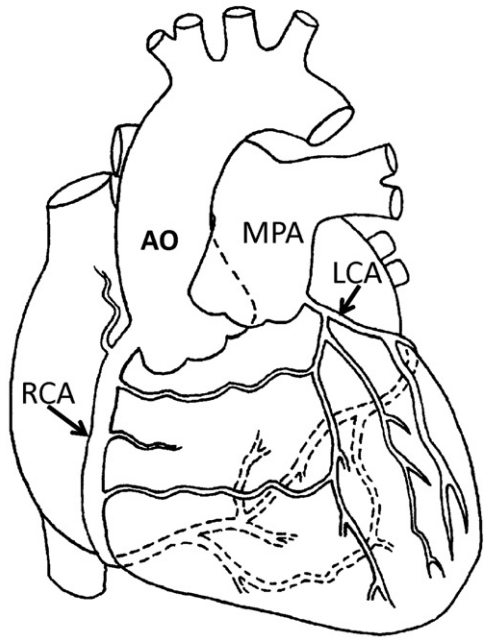

Fig. 1. Schematic diagram representing ALCAPA. ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; AO, ascending aorta; LCA, left coronary artery; MPA, main pulmonary artery; RCA, right coronary artery.

main pulmonary artery. Cineangiography with dye injection into the ascending aorta will demonstrate opacification of a dilated RCA, which will give off collateral arteries at various points along its route to the LCA (**Fig. 2**). The direction of the flow in the LCA is retrograde and drains into the main pulmonary artery.

Differential diagnosis of ALCAPA includes acute myocarditis, cardiomyopathy, and severe forms of left heart obstruction such as congenital aortic stenosis or coarctation of the aorta.

Management

History of episodic respiratory distress with effort such as feeding, physical findings of pallor, wheezing, tachycardia, and ECG findings of ischemic changes and chest radiograph evidence of cardiomegaly with passive congestion raise an index of suspicion for this diagnosis. Definitive diagnosis relies on imaging studies such as echocardiography or cineangiography. A 2D-echocardiographic image of the LCA alone may be misleading, because there may be false continuity between the aorta and LCA. However, with color Doppler interrogation with Nyquist limit set to a low velocity, flow signal may detect retrograde direction of LCA flow with continuity to the main pulmonary artery, which is characteristic of this lesion. The life-threatening nature of this anomaly demands judicious medical stabilization and rapid transportation to a tertiary pediatric facility, so that surgery is performed. Currently, the preferred surgical approach is removal of the ALCAPA and reimplantation into the aorta. Because of ischemic myocardial injury, the postoperative course may be quite stormy due to hypotension and frequent arrhythmia. In some patients, extracorporeal membrane oxygenator support may be necessary until LV function recovers sufficiently. After a two coronary artery system is established and

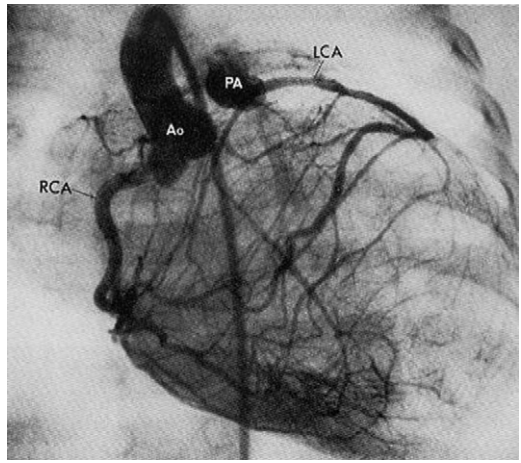

Fig. 2. Cineangiogram of ALCAPA. The catheter tip is in the AO. The RCA is dilated. There are numerous collateral vessels between RCA and LCA. LCA opacifies retrograde and empties into the main pulmonary artery (PA). ALCAPA from the main pulmonary artery is redundant.

the patient survives the postoperative period, his or her myocardial function may improve steadily.[4] However, depending on the size of infarcted fibrotic segment and surrounding peri-infarct ischemic area in the myocardium, the patient must be carefully monitored for recurrent ventricular arrhythmia. A patient with a large devitalized myocardial segment forming an aneurysm is particularly vulnerable to sudden onset of ventricular tachycardia or fibrillation months or years later. These patients may require Holter monitoring and, if indicated, an implantable defibrillator.

Origin of a Coronary Artery from the Wrong Aortic Sinus with its Course Between the Aorta and the Pulmonary Artery

Unfortunately, these cardiac anomalies seldom give warnings before a catastrophic event, frequently on an athletic field. They are often diagnosed postmortem after sudden unexpected cardiac death in athletes, and are the second most frequent cause of such death behind hypertrophic cardiomyopathy.[5] Of the two types of anomalies depicted in **Fig. 3**, the origin of the LCA from the right aortic sinus is more frequently lethal. The prevalence of sudden athletic field deaths due to all causes is estimated to be 0.5 per 100,000 per year among high school age athletes in the United States.

Postmortem examinations have shown an acute angle take-off of the anomalous coronary artery with a slit-like ostium located in the inappropriate aortic sinus. The proximal course of the anomalous artery lies between the aorta and pulmonary artery. It may be intramural (within the muscular layer of the aortic wall itself) or free in the space between the great arteries. Typically no atheromatous plaques have been found. Such an anomalous coronary artery may be able to provide adequate myocardial perfusion at rest such that the patients are asymptomatic. However, during strenuous activities, because of the narrow slit-like orifice, the intramural or interarterial course of the vessel, the aberrant coronary artery may be incapable of providing coronary blood flow commensurate with the subject's demand for increased myocardial perfusion, thus producing sudden ischemia, which in turn may lead to onset of ventricular fibrillation or cardiac standstill. Systolic engorgement of the aorta and the pulmonary artery due to increased stroke volume may further compromise the coronary artery caliber.

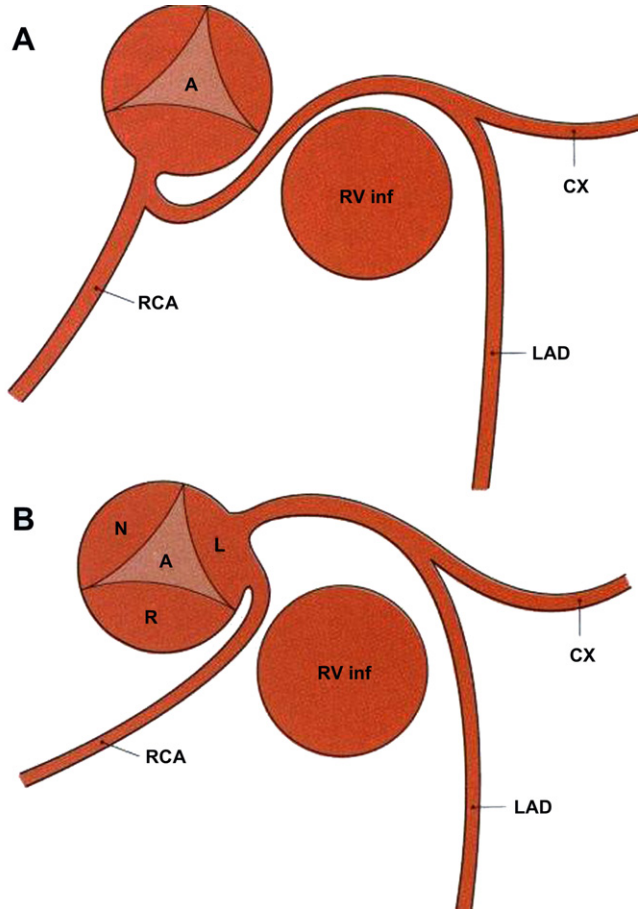

Fig. 3. Two types of aberrant coronary artery from "wrong sinuses." Each shows the aortic valve with its 3 sinuses, right ventricular infundibulum, and two coronary arteries. Top of the diagram is posterior, bottom is anterior, left of the diagram is right side, right of the diagram left side. (*A*) Origin of the LCA from the right sinus of Valsalva, coursing between the aorta and the pulmonary artery. Although in this diagram, the two coronary arteries share a common ostium, actual cases vary in anatomy. Sometimes the LCA ostium is slit-like. The initial segment of LCA may be intramural (embedded within the aortic wall). (*B*) Origin of the RCA from the left sinus, coursing between the two great arteries. L, left coronary sinus; N, noncoronary sinus; R, right coronary sinus; RV inf, right ventricular infundibulum. (*From* Lieberthson R. Congenital anomalies of the coronary arteries. In: Gatzoulis MA, Webb GD, Daubeney PEF, editors. Diagnosis and management of adult congenital heart disease. Philadelphia: Churchill Livingstone; 2003. p. 425–31; with permission.)

Management

These anomalies are rarely suspected or diagnosed in life. ECG or stress tests may not yield abnormal results. Some of the athletes have noted syncope or chest pain in the preceding 24 months of the final catastrophic event. If healthy young patients complain of such symptoms, they should be explored carefully, including imaging studies for coronary arteries first with transthoracic echocardiography specifically focused on coronary artery origins. If the patient's body habitus does not allow clear visualization of his or her coronary arteries, multidetector CT scan will demonstrate

clear images albeit at the cost of added expense and radiation exposure. Also, it is highly recommended that when an echocardiogram is ordered for a young patient for any other clinical indications, the interpreting cardiologist and the sonographer verify origins and distributions of the RCAs and LCAs. This is not yet a uniformly established standard for sonographers, but every now and then an aberrant coronary artery is incidentally discovered.

Surgical "unroofing" of the intramural coronary artery segment to move coronary orifice to a more normal position and at the same time widen the orifice area has been done successfully.[6]

CORONARY ARTERY COMPLICATIONS ASSOCIATED WITH CONGENITAL HEART DISEASE

Coronary Artery Obstruction After Arterial Switch Operation for D-Transposition of the Great Arteries

Complete transposition (or D-transposition) of the great arteries (DTGA) is one of the more common cyanotic heart disease with prevalence of 20 to 30 per 100,000 live births. Without prompt treatment, about 90% of these babies will die within the first year of life. This anomaly may exist alone or in association with a ventricular septal defect, coarctation of the aorta, or other cardiac anomalies. Because of low oxygen saturation noted by bedside pulse oximetry, the patient should receive echocardiography or be referred to a cardiologist within a few days after birth. Once diagnosed, a baby with DTGA can be stabilized using prostaglandin infusion and transported to a tertiary facility. There, the patient undergoes either balloon atrial septostomy (Rashkind procedure) or is brought directly to the operating room for an arterial switch procedure.

As part of this operation the surgeons truncate both great arteries near their origins from the ventricles, and move the RCAs and LCAs from the original aorta to the new aorta (native main pulmonary artery root). There are at least nine anatomic variations in the way the two coronary arteries arise from the native aorta.[7] Since the inception of arterial switch operations in the mid-1980s, congenital heart surgeons have improved the technique of transposing coronary arteries. In cases of "usual" coronary artery pattern (RCA from the posterior right-facing aortic cusp and LCA from the posterior left-facing cusp) the surgeon will remove the RCAs and LCAs from the old aortic root together with a small piece of surrounding aortic wall (so-called button), and move them to the new aortic root. In patients with more complex or unusual coronary pattern the surgeon must use innovative techniques of switching the coronary arteries. In those patients with unusual coronary artery distribution, there appears to be a higher risk of postoperative ischemia due to kinking or stretching of the arteries. Most of the survivors of the arterial switch operation are asymptomatic. Nevertheless, some patients, especially those with originally unusual coronary artery distribution, have had less-than-normal coronary flow reserve.[8,9] The clinical significance of these findings is not fully understood.

Management

It is important to encourage survivors of the arterial switch operation to seek periodic cardiac evaluation on a life-long basis. Also, the primary care physician should emphasize heart healthy life-style and dietary habits in these children so as to minimize accumulation of coronary risk factors as they grow into adolescence and adulthood. Those who have demonstrated coronary obstruction require more frequent and intensive follow-up evaluations.

Coronary Artery Damage Associated with Repair of Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most frequently encountered cyanotic heart disease. Its prevalence is estimated to be 26 to 48 per 100,000 live births. Timing of corrective surgery is dictated by several anatomic features. In the presence of pulmonary atresia, marked hypoplasia of the pulmonary arteries or presence of large collateral arteries from the aorta to the pulmonary arteries, the patient may have to undergo one or more palliative operations before corrective surgery is done.

Corrective surgery for TOF includes patch-closure of the ventricular septal defect and widening of the right ventricular outflow tract by infundibular muscle resection combined with either a patch placement across the pulmonary valve annulus (so-called transannular patch) or use of a prosthetic conduit from the RV to the pulmonary artery. There are known aberrant coronary artery patterns associated with TOF. Origin of the anterior descending branch from RCA has been reported to occur in 5% of TOF patients.[10] A large conus branch, or an accessory LAD present in about 15% of TOF patients, runs across the face of the right ventricular outflow tract (infundibulum) and may be inadvertently damaged during the surgery. If such an arterial branch subtends a large myocardial territory, the patient may suffer from clinically significant myocardial infarction and myocardial conduction delay, both of which may reduce the overall cardiac function in the future. In general, postoperative TOF patients are more likely to develop global RV or LV dysfunction, right heart enlargement, right bundle branch block, and sustained or intermittent arrhythmia than to develop localized myocardial ischemia or myocardial infarction.[11]

Management

Patients with postoperative tetralogy must be followed, by a cardiologist experienced in congenital heart disease, at regular intervals on a life-long basis for surveillance of the right ventricular size and function, volume overloading due to pulmonary regurgitation, and propensity for cardiac arrhythmia. In addition they should be given the same advice as the aforementioned DTGA patients; that is, the need for heart healthy life-style.

Coronary Artery Ostial Stenosis Associated with Supravalvar Aortic Stenosis (Isolated or in Association with Williams Syndrome)

Supravalvar aortic stenosis (SVAS) is caused by localized or diffuse narrowing of the ascending aorta starting at the junction between the sinuses of Valsalva and the tubular portion of the ascending aorta (**Fig. 4**). It may occur alone or in association with pulmonary artery stenosis. It is often a cardiac phenotype of Williams syndrome. The genotype of Williams syndrome is deletion of 7q11.23, the segment that includes elastin gene.[12] Prevalence of Williams syndrome is estimated to be 1 in 20,000 live births, and is characterized by SVAS, peripheral pulmonary artery stenosis, developmental delay, and social and friendly personality traits. There are at least four factors in this condition which contribute to myocardial ischemia. First, deficiency of elastin in the aortic wall causes loss of Windkessel effect, whereby part of the energy carried by the ejecting blood is stored during systole and released back during diastole. Without it there is wider pulse pressure and low diastolic pressure, impairing coronary perfusion. Second, deficiency of elastin also causes proliferation of smooth muscle cells in the arterial walls, causing medial thickening of the aorta and its branches, including coronary arteries. This has an effect of increasing impedance to forward aortic flow. Third, development of obstructive supravalvar ridge further increases LV afterload and stimulates LV myocardial hypertrophy. Pulmonary artery obstruction, likewise, causes RV hypertrophy. Biventricular hypertrophy tends to increase oxygen demand. Fourth, abnormally shallow sinuses of Valsalva with prominent ridge restrict

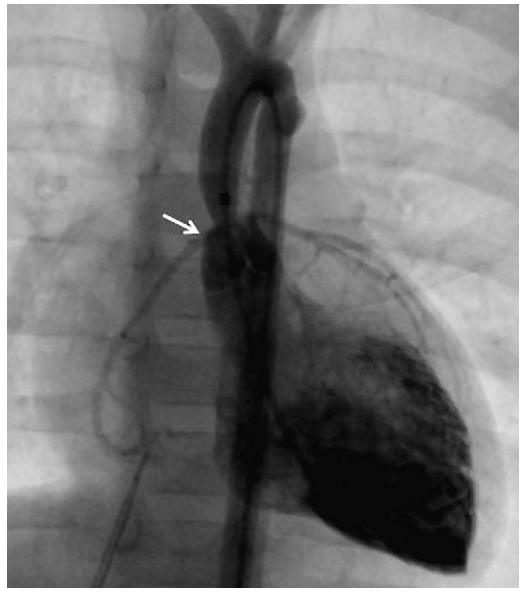

Fig. 4. Cineangiogram of supravalvar aortic stenosis. Contrast injection was made with the catheter tip in the LV. Note abrupt narrowing of the junction between and sinuses of Valsalva and the tubular portion of the ascending aorta. The two coronary arteries arise at the junction. Commissures between the aortic valve leaflets are located near or at the sinotubular junction. Valve motion may interfere with coronary inflow. In some cases, anatomic stenosis of one or both coronary ostia occurs. The white arrow indicates right coronary ostium.

excursion of the aortic leaflets. The valve leaflets are thus unable to fully open into positions paralleling the blood flow axis, and may obstruct the coronary ostia. Duration of diastole may be shortened owing to prolonged systolic ejection time, reducing myocardial perfusion. Exposure of the coronary arteries to high pressure proximal to the aortic stenosis may contribute to progressive coronary artery pathology. Ostia of the coronary arteries, especially the left coronary ostium frequently becomes stenotic. There have been reports of sudden death of patients, presumably due to sudden myocardial ischemia. Risk of sudden death in this condition is estimated to be 1/1000 patient years as compared with 0.01–0.04/1000 patient years in general population. This risk does not appear to correlate with the severity of aortic obstruction but appears to be related to bilateral ventricular hypertrophy and coronary artery stenosis.[13] Furthermore, sudden death in Williams syndrome and, to a lesser extent, in isolated SVAS have occurred during cardiac catheterization or noncardiac operation under sedation or general anesthesia.[13] Based on analysis of 19 cases of sudden cardiac deaths in Williams syndrome, Bird and colleagues[14] concluded that presence of biventricular outflow tract obstruction combined with coronary artery abnormalities carried the highest risk of sudden death.

Management

In this condition, potential for myocardial ischemia exists without overt hemodynamic abnormalities. Thus, the patient may not show any alarming symptoms. ECG or echocardiographic findings may be insensitive for prediction of sudden ischemic event. Thus, completely elective surgery needs to be weighed against this possibility.

Traditionally, surgical correction in the form of patch aortoplasty, more recently symmetric patch technique of Brom, is considered, when the pressure gradient from the LV to the ascending aorta exceeds 40 to 50 mmHg. Whereas adequate imaging of the coronary arteries is desirable either by cardiac catheterization and or less invasive multidetector CT scan or MRI, these tests in themselves carry greater than usual risks. Repair of coronary oxtail stenosis is challenging but it has been done successfully.[15]

Coronary Artery Obstruction Associated with Pulmonary Atresia with Intact Ventricular Septum

Hypoplastic right heart syndrome is characterized by an abnormally small RV, which is unable to support normal pulmonary blood flow on its own accord (**Fig. 5**). Tricuspid atresia and pulmonary atresia are two major variants of this syndrome. A subset of pulmonary atresia with intact ventricular septum with a patent but small tricuspid valve may produce a network of vascular channels (called sinusoids) communicating the right ventricular lumen to one or both of the pericardial coronary arteries. With systemic or suprasystemic systolic pressure within the right ventricular cavity, blood flow in these fistulous connections may compete with the normal coronary blood flow originating in the ascending aorta. Sometimes, these competing blood coronary streams may cause tortuosity, severe intimal proliferation with obstruction, such that portions of the myocardium may be dependent on the RV-originated coronary flow (so-called RV-dependent coronary circulation).[16]

Patients with pulmonary atresia and intact ventricular septum usually undergo an initial surgical palliation in the form of modified Blalock-Taussig shunt with or without pulmonary valvotomy. This latter procedure is to allow resumption of some RV pumping function. In some centers, pulmonary valvotomy may be done as a transcatheter intervention.

Those patients who do not have any functioning RV, in effect, have single ventricle physiology, and are consigned to eventual Fontan procedure, whereby both superior and inferior vena cava (SVC, IVC) are anastomosed to the pulmonary artery. On the other hand, those with a relatively mild degree of RV hypoplasia and amenable to

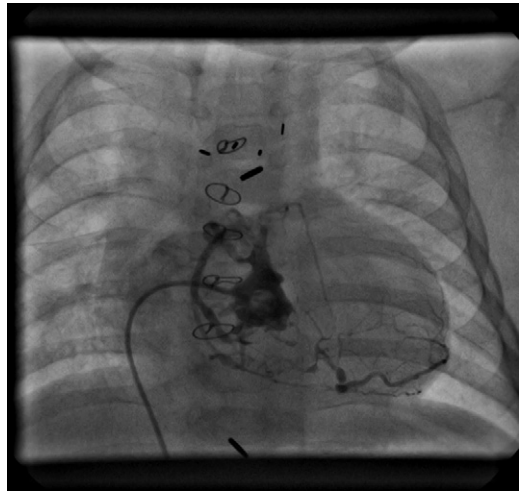

Fig. 5. Cineangiogram with injection inside the hypoplastic RV with pulmonary atresia. Sinusoids connecting RV to both coronary arteries are clearly seen.

pulmonary valvotomy may receive only Glenn anastomosis between the SVC and right pulmonary artery, so that only the blood return from IVC is pumped by the small RV into the pulmonary artery (so-called one-and-a-half ventricle repair). Pulmonary valvotomy may produce sudden decompression of the RV pressure. If such a patient has an unsuspected RV-dependent coronary circulation with no adequate aorta-originated blood supply to a portion of the myocardium, that patient may suffer from myocardial ischemia and heart failure as a result. In some cases, thrombosis within the abnormal coronary artery has caused myocardial infarction. Coronary artery stenosis associated with pulmonary atresia may be progressive over time, so that the patients with demonstrated sinusoidal connection between RV and epicardial coronary arteries should have follow-up imaging studies. In some cases, heart transplantation may be the only viable therapy.

Management

The subset of patients with hypoplastic right heart syndrome with known coronary artery stenosis or complete occlusion need to be followed closely for any progressive myocardial ischemia, and the patients and families must be made aware of the increased risk of cardiac events in the future. However, most patients with pulmonary atresia with intact septum, who undergo a Fontan operation have good short- and intermediate-term survival.

Coronary Artery Sequelae of Kawasaki Disease

Kawasaki disease (KD) is an immune-mediated vasculitis affecting medium-sized arteries, most prominently coronary arteries. Epidemiologic findings suggest that KD is triggered by one or more widely distributed infectious agents in a genetically predisposed child.[17] It attacks mostly children under 5 years of age, more in males than females with a ratio of 1.5 to 1. The highest prevalence is found among children of East Asian backgrounds (Japanese, Korean, and Chinese), the lowest among white children, and intermediate among African American children. The disease occurs most frequently in the winter and spring in temperate zone countries.[18,19]

Despite extensive searches for a specific causal agent by many investigators in the 33 years since the original description of the disease,[20] no cause has been established. Currently prevailing theory is that there is genetic propensity in a segment of population to develop vasculitic cascade through expression of proinflammatory proteins and promoters, triggered by one or more ubiquitous infectious agents either viral or bacterial in nature. A consortium of researchers are involved in genome-wide search for a set of mutations coding for these host factors.[17,21]

Diagnosis is made by fulfillment of principal clinical criteria. Diagnosis of KD requires the presence of fever lasting 5 or more days, and at least four of the five following physical findings, without another explanation:

Conjunctival injection, usually without discharge
Oral mucous membrane changes, such as red, cracked, dry lips or strawberry tongue
Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet
Rash (nonvesicular)
Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter).

About 15% of the patients do not fulfill four of the five requisite criteria, and are classified as atypical or incomplete Kawasaki disease. Recent management

guidelines copublished by the American Heart Association and the American Academy of Pediatrics,[22] show a diagnostic algorithm using acute phase reactants (elevated C-reactive protein and erythrocyte sedimentation rate) and supplementary laboratory tests serum albumin less than 3 g/dL, anemia for age, elevated alanine aminotransferase, and platelet count after 7 days greater than 450,000/mm^3 to assist clinicians to arrive at a working diagnosis of KD within 7 to 10 days of fever onset. This should allow that intravenous immunoglobulin and aspirin therapies may be instituted in time to prevent coronary artery sequelae. This diagnostic strategy appeared to be useful in identifying 97% of the patients within the time window for intravenous immunoglobulin (IVIG) treatment according to a retrospective chart review of nearly 200 patients with typical and incomplete KD patients from four centers.[23]

Before the widespread use of IVIG therapy, about 20% of the KD patients developed coronary artery aneurysms. With timely (within 10 days of fever onset) IVIG treatment, the prevalence of aneurysms has been reduced to about 5% and, most importantly, giant aneurysms (>8 mm in diameter) prevalence has been reduced to less than 1%. Approximately 50% of the aneurysms, particularly small-to-medium sized aneurysms (3–6 mm in diameter) undergo a process of regression such that the coronary artery lumen becomes normal.[24] However, this regression seems to be the result of migration of smooth muscle cells from outer layers into the intimae and subsequent proliferation forming a thick neointima. Thus, these regressed arteries possess abnormal wall thickness and reduced response to various vasodilators.

Myocardial ischemia occurs in patients with KD owing to occlusion or critical narrowing of one or more coronary arteries through three different mechanisms.

Thrombotic Occlusion of Coronary Artery Aneurysm

The earliest stage of KD is characterized by microangiitis of many organs, including the skin and mucous membranes. Ten to 12 days into the illness, panvasculitis of major coronary arteries begins. In some patients, the coronary arterial walls, weakened by inflammation, yields to expansile force of the arterial pressure, and becomes an aneurysm. A combination of resultant flow stagnation, activated procoagulant endothelium, and increased number and activity of platelets collaborate to produce thrombotic occlusion, leading to myocardial infarction (**Fig. 6**). Patients with aneurysm diameter greater than 8 mm (giant aneurysm) are more likely to develop thrombotic occlusion starting in the acute of illness.[25] Myocardial infarction is most likely to occur within the first year after onset of KD.[1,25]

Management

Patients with large coronary artery aneurysms can be protected from thrombosis with anticoagulant therapy using warfarin (with a target international normalized ratio of 2.0–2.5) and aspirin 3 to 5 mg/kg per day.

Some patients develop thrombosis within the coronary artery lumen despite anticoagulation. Recognized in time, such a patient may be rescued with thrombolytic therapy using tissue plasminogen activator or another agent, followed by heparin infusion. With early detection of coronary artery aneurysms and timely treatment with IVIG, there has been a dramatic decrease in the number of giant aneurysms and acute myocardial infarction during the acute illness. Once the occluding thrombus becomes organized, and there are no adequate collateral vessels to ameliorate ischemia, coronary artery bypass graft may be the only solution. Attempts to surgically remove or trim down the giant aneurysm have met with mixed results thus far.

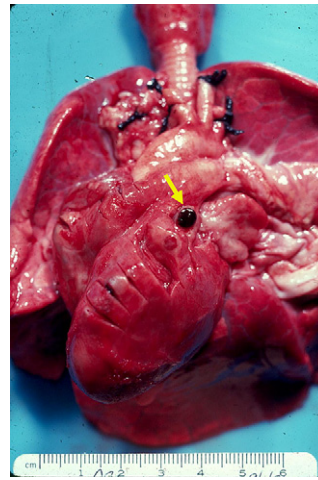

Fig. 6. Autopsied heart of a 3-month-old girl who died of myocardial infarction 3 weeks after the onset of Kawasaki disease. Both coronary arteries had formed giant aneurysms (*arrow* shows aneurysmal left coronary artery filled with clot). The LCA aneurysm was completely occluded with old and fresh clots.

Coronary Artery Stenosis Due to Neointimal Proliferation

During the subacute phase of the disease, there is neointimal thickening as a result of migration of smooth muscle cells and fibroblasts from media to intima of the vessel wall. Fifty percent or more of the original coronary artery aneurysms undergo complete regression or normalization of the lumen size, although both the wall structure and vasoreactivity of the coronary artery segment remains abnormal. Similar process may occur locally at the entrance or exit point of the aneurysm, causing localized stenosis. When the stenosis becomes severe, this may cause myocardial ischemia. Again, depending on whether there are enough collateral channels to compensate for the ischemia, some type of revascularization procedure should be considered.

Management

Bypass graft surgery using arterial grafts have been successful. Kitamura and colleagues[26] reported a graft patency rate of 95% over 20 years in a cohort of 114 children and adolescents. However, the cardiac event-free rate has declined over time. Percutaneous balloon angioplasty alone is unlikely to succeed in the presence of dense scar tissue and calcification. Rotational ablation with or without stent placement has been used with short-term success in Japan.[27] However, there were cases of restenosis or formation of new aneurysms at the site of intervention, often requiring repeat intervention or surgical revascularization (**Fig. 7**).

Obliterative Coronary Arteritis Without Large Aneurysm

This is a rare complication of KD with only a few reported cases.[28–30] Typically, the patient is known to develop diffuse mild-to-moderate coronary artery dilation. In time, the coronary arteries appear to undergo regression, then acute chest pain, respiratory distress or abdominal pain occurs, and the patient dies unexpectedly. Postmortem examination would show almost complete obliteration of the coronary artery lumen due to excessive proliferation of neointimal cells surrounded by copious intracellular matrix (**Fig. 8**).

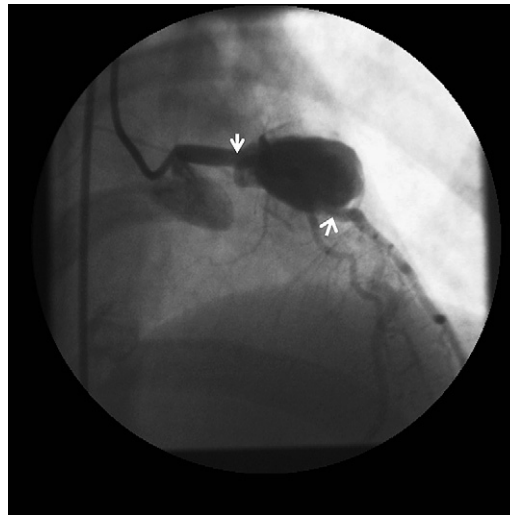

Fig. 7. Cineangiogram showing a giant aneurysm of the LAD of 2-year-6-month-old boy 5 months after the onset of Kawasaki disease. The two arrows indicate entrance and exit points of the saccular aneurysm, where localized stenosis may occur due to intimal proliferation.

Management

Because this process occurs diffusely over long segments of arteries, currently there is no effective therapy. In cases, where the obliterative process is confined to a short segment, surgical treatment may be improvised on a case-by-case basis.

Myocardial Ischemia Associated with Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetically determined myocardial hypertrophy far exceeding the degree of LV hypertrophy necessary to sustain the usual amount of work load (**Fig. 9**). Its incidence is estimated to be as high as 0.2% of population in all ages.[31] However, it is relatively rare in the pediatric population. Typically the onset is gradual and full clinical manifestation may not occur until the teenage years and young adulthood. There is global hypertrophy of ventricular walls, but hypertrophy is often quite remarkable in the ventricular septum.

In a subset of patients, there is dynamic obstruction of the left ventricular outflow tract due to the combination of asymmetric septal hypertrophy (ASH) and abnormal systolic anterior motion (SAM) of the mitral anterior leaflet. These morphologic changes can be easily diagnosed by routine echocardiography. ECG almost always shows abnormal left ventricular hypertrophy accompanied by ST segment and T wave changes, indicative of global ischemia. Microscopically, there is extensive disarray of myocardial muscle fibers. As the disease advances, there will be increasing fibrosis within the myocardium probably related to a relative paucity of intramyocardial nutrient arteries. Occasionally, there is an associated myocardial bridge, in which a segment of an epicardial major coronary artery, most typically the LAD, tunnels through the myocardium for a short distance. During systole, myocardial contraction may “pinch off” that section of the coronary artery lumen, and may cause decreased flow. The role of myocardial bridge in causation of myocardial ischemia is being debated.[32,33] Intramyocardial fibrosis may be delineated by MRI using late gadolinium enhancement imaging technique relatively early in the course of HCM.[34] This

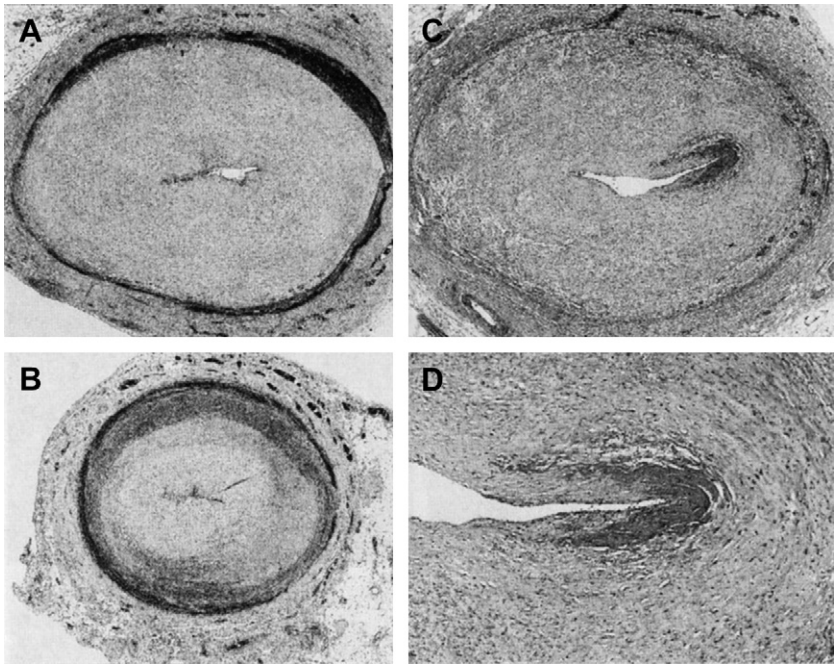

Fig. 8. Photomicrograms of epicardial coronary arteries of a 4-year-old boy with a febrile illness with conjunctivitis, pharyngitis, rash, and lymphadenopathy 7 months before death, followed by multiple episodes of abdominal pain requiring repeated hospital admissions. There is diffuse severe fibrointimal proliferation with marked luminal narrowing of (*A*) the left main, (*B*) LCX, and (*C*) RCA. (*D*) The right coronary artery demonstrated a small thrombus (high magnification). Multiple areas of medial destruction as well as infiltrating numerous CD4+ and CD8 + T lymphocytes and rare B cells. (*From* Burke AP, Virmani R, Perry LW, et al. Fatal Kawasaki disease with coronary arteritis and no coronary aneurysms. Pediatrics 1998;101:109; with permission.)

technique makes use of the phenomenon in which intravenously injected gadolinium chelate lingers in fibrous tissue long after its level in the surrounding metabolically active tissue has declined. Its application began in patients with myocardial infarction due to coronary artery disease.

Patients with severe HCM may be asymptomatic or may show a variety of symptoms, including easy fatigue, chest pain (ranging from sharp transient atypical pain to typical angina pectoris), palpitations, and syncope. This diagnosis should always be considered when a young athlete or teenager complains of chest pain with exertion. Sudden cardiac death due to HCM is estimated to be 2% to 4% per year. It is the leading cause of sudden cardiac death in young athletes. The cause of death is attributed to onset of ventricular fibrillation due to localized myocardial ischemia.

In a subset of patients, there is dynamic obstruction of the left ventricular outflow tract due to a combination of ASH and abnormal SAM. These morphologic changes can be easily diagnosed by routine echocardiography.

Management

A β-adrenergic blocking agent is the mainstay of therapy for HCM. Its effects include reducing myocardial oxygen consumption and ameliorating hyperdynamic myocardial contraction, thus reducing the outflow tract pressure gradient. Those patients with

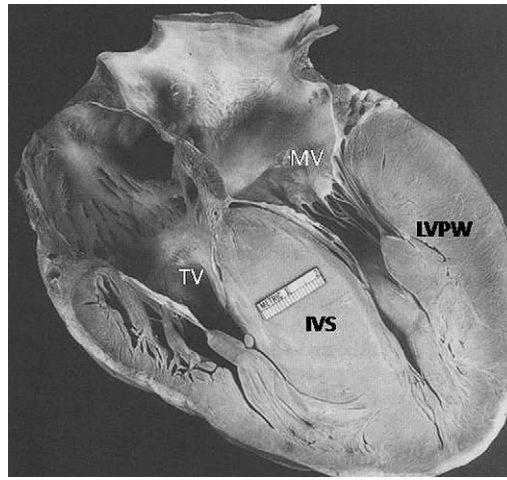

Fig. 9. Autopsy photo of an adult with hypertrophic cardiomyopathy. The heart has been sectioned to show atrial and ventricular septa, mitral (MV) and tricuspid valves (TV). Note marked hypertrophy of the interventricular septum (IVS) and the LV posterior wall (LVPW), and moderate hypertrophy of the RV. (*From* Sorajja P, Nishimura RA. Hypertrophic cardiomyopathy. In: Gatzoulis MA, Webb GD, Webb, et al, editors. Diagnosis and management of adult congenital heart disease. Philadelphia: Churchill Livingstone; 2003. p. 425–31; with permission.)

dynamic LV outflow obstruction may benefit from surgical myotomy and myectomy. Those patients considered to be at high risk of sudden death may received implantable cardiac defibrillators.

Acute Coronary Syndrome Associated with Cocaine Use

Abuse of illicit drugs has become a major problem that pediatricians cannot avoid in their teenage patients. Although many street drugs and prescription drugs taken by patients without medical supervision may cause cardiovascular-related problems, cocaine stands out as the drug most likely to cause direct myocardial ischemia and death. An estimated 8 million individuals use it on a regular basis in the United States. As many as 25% of patients that present to urban hospitals with nontraumatic chest pain have detectable cocaine or its metabolites in their urine. Cardiovascular effects of cocaine may be due to inhibition of presynaptic uptake of adrenergic neurotransmitters, resulting in tachycardia, hypertension, and coronary artery spasm. Chronic use of cocaine is associated with accelerated atherosclerosis, endothelial dysfunction, and increased inflammatory markers, which may lead to acute coronary syndrome.[35,36] Cocaine toxicity may precipitate seizures, and respiratory and circulatory depression. Cocaine is also highly pyrogenic because of increased muscular activity. Heat loss is inhibited by the intense vasoconstriction. Cocaine-induced hyperthermia may cause muscle cell destruction and myoglobinuria resulting in renal failure.

Acute coronary syndrome is associated with chest pain (typical or atypical), ST-segment elevation of ischemic type on presentation, and elevation of troponin or creatinine kinase MB fraction within 24 hours of presentation.

Management

Patients presenting with chest pain should receive careful history-taking (including crucial social history) and physical examination. Patients with chest pain related to

cocaine often present with agitation, anxiety, tachycardia, and hypertension. Toxicologic screening must be done if drug abuse is suspected. The patient should be observed in the ICU or cardiac care unit. Treatment should include benzodiazepine, aspirin, supplementary oxygen, and an ACE-inhibitor. In addition, a calcium channel blocker such as diltiazem is useful to counteract or prevent coronary vasospasm. There is controversy regarding the use of a β-adrenergic blocker in this setting, because of fear that possible overactive α-adrenergic effect of cocaine may cause hypertension and coronary vasospasm. Hoskins and colleagues[37] have reported that labetalol, a balanced α and β blocker has shown favorable outcomes in terms of improvements in hemodynamics as well as inflammatory markers.

GENERAL STRATEGY FOR MANAGEMENT OF CARDIAC CRISIS WITH POSSIBLE MYOCARDIAL ISCHEMIA

Although myocardial ischemia is not an everyday pediatric problem, it may presents itself unexpectedly and, therefore, it causes an inordinate amount of confusion and anxiety for those called upon to manage it. First, early recognition of the problem is important.

Infants with severe myocardial ischemia such as those with ALCAPA may, in its early stage, show episodic pain and distress but gradually change into persistent symptoms of heart failure with progressive respiratory distress, tachycardia, and failure to thrive. A heart murmur is either absent or only faintly audible. Heart tones are often distant, reflecting weakened myocardial contractility. Grunting and retractions may be present. When a cardiac problem is suspected, the primary care physician must obtain basic studies, including chest radiograph and ECG. If these tests show abnormal findings, the patient must be referred promptly to a pediatric cardiologist. Initial echocardiogram should focus on evaluation of cardiac chamber size and function as well as presence or absence of pericardial effusion. More detailed echocardiographic examination can be undertaken by the cardiologist, looking for specific diagnosis.

Upon witnessing a patient with cardiorespiratory distress, the physician must first establish adequate airway and support ventilation. Then, proceed to evaluate the presence and quality of peripheral pulses, to determine whether full-scale cardiopulmonary resuscitation is needed. After having ruled out more common problems such as heat exhaustion, asthmatic attacks or panic attacks, the physician must entertain the possibility of a cardiac event. Inappropriate tachycardia, hypotension, and anxiety may be a tip-off. Chest pain may or may not be present. In young children, myocardial ischemia may cause nausea, vomiting, and abdominal pain.

If an older child is brought in with a cardiorespiratory crisis, airway, breathing, and cardiac function must be immediately assessed, and supportive or resuscitative measures must be taken. After a team of care-givers has been organized, the clinician must obtain a careful history exploring suspected heart disease, past cardiac surgery, or possible prolonged febrile illness accompanied by skin rash, conjunctivitis, and oral mucous membrane lesions (possible missed Kawasaki disease).

The physician must explore possible recent syncope or seizure (especially any without warning). After establishing some rapport with the patient, the physician must also ask, as delicately as possible, about substance use, for the purpose of eliciting specific drugs involved.

The physician must also explore the possible family history of syncope, seizures, or sudden cardiac deaths especially among the first-degree relatives. In examining the patient, begin by looking for obvious dimorphisms, such as Williams syndrome.

The patient's distress must be alleviated with supplemental oxygen and analgesics, as needed. Basic 12-lead ECG, chest radiograph, and echocardiogram may further

elucidate the problem. Venipuncture to start a peripheral intravenous line should be combined with obtaining creatinine phosphokinase subfractions and troponin levels, as well as other routine laboratory tests. These biomarker levels and ECG must be repeated periodically to establish a time course of myocardial damage.

If cocaine or other recreational drug use is suspected, toxicologic screening tests should be obtained.

Judicious incremental fluid management is important to remedy hypovolemia and, at the same time, prevent overloading the weakened heart.

When cardiac ischemia is strongly suspected, a pediatric cardiologist must be consulted. A speedy transfer to a tertiary care center must be arranged. The primary task of the pediatric cardiologist is to arrive at an accurate anatomic and physiologic diagnosis as to the cause of ischemia and plan a definitive therapeutic course to remove its source. In many cases surgical therapy is clearly indicated. In other situations, medical management can be adopted while surgical options are being weighed.

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