Coronary artery anomalies (CAAs) are a diverse group of congenital disorders whose manifestations and pathophysiological mechanisms are highly variable. The subject of CAAs is undergoing profound evolutionary changes related to the definition, morphogenesis, clinical presentation, diagnostic workup, prognosis, and treatment of these anomalies. To understand the clinical impact of CAAs, the fundamental challenge is the firm establishment, for a particular type of CAA, of a mechanism capable of interference with the coronary artery’s function, which is to provide adequate blood flow to the dependent myocardium. The present review focuses on anomalous origination of a coronary artery from the opposite sinus—the subgroup of CAAs that has the most potential for clinical repercussions, specifically sudden death in the young. For this subgroup, solid diagnostic screening protocols should be established, especially for athletes and other young individuals subjected to extreme exertion. Intravascular ultrasonography is the preferred means to evaluate the mechanisms responsible for ischemia in anomalous origination of a coronary artery from the opposite sinus and other potentially significant CAAs. Patients symptomatic of anomalous origination of a coronary artery from the opposite sinus may undergo medical treatment/observation, coronary angioplasty with stent deployment, or surgical repair. To be competent to advise CAA carriers, especially in the context of sporting or military activities, cardiologists should undergo specific training in these disorders. Only multicenter collaboration on protocols dedicated to CAAs can give rise to the large-scale studies needed to define the prognosis and optimal treatment of these disorders. (Circulation. 2007;115:1296-1305.)

Key Words: coronary disease ■ death, sudden ■ diagnosis ■ heart defects, congenital ■ ischemia

The subject of coronary artery anomalies (CAAs) is undergoing profound evolutionary changes related to the definition, morphogenesis, clinical presentation, diagnostic workup, prognosis, and treatment of these anomalies. Initially, CAAs were the subject of anatomic discussions that centered around the description and classification of unusual morphologies. Eventually, the ischemic mechanisms of CAAs and the incidence of these anomalies in the normal human population were addressed in autopsied patients and coronary angiography populations. More recent studies have dealt with vexing questions related to pathophysiological mechanisms and clinical prognoses for different forms of CAAs. The present review focuses on anomalous origination of a coronary artery from the opposite sinus (ACAOS) with intussusception of the ectopic proximal vessel, which is the subgroup of CAAs that has the most potential for clinical repercussions, specifically sudden death in the young.

Definition of Coronary Anomalies

Classification criteria for CAAs have been extensively discussed in the literature. Some authors prefer to categorize CAAs only as “major,” “severe,” “important,” or “hemodynamically significant” anomalies versus “minor” ones. Our group has concluded that a comprehensive and widely agreed-upon scheme to define and classify CAAs should initially consider all possible coronary anatomic variations independently from the clinical and hemodynamic repercussions of individual CAAs. Such a scheme should include 2 basic steps: (1) The normal coronary anatomy (Table 1) should be described in terms of quantitative and qualitative criteria, and (2) once the normal features have been excluded, the remaining features should be considered to define abnormality and should be used to generate a classification order.

The basic issue in the definition of a normal coronary artery (and, hence, an anomaly) is the normal spectrum of variation. For example, whereas most experts agree that the normal spectrum of variants. We have proposed that, when possible, one should use quantifiable criteria such as, “Any
form observed in >1% of an unselected general population is normal."11 The literature continues to entertain these and similar considerations while the field awaits a widely accepted endorsement by representative professional groups.10,16

Table 2 shows our group’s proposed comprehensive classification scheme. A basic principle of coronary classification should be that the nature and name of a specific coronary artery are assigned, not according to the site of origin or proximal course, but according to the dependent territory. Figures 1 and 2 show 2 complex CAAs that exemplify the methods used to describe any given complex case.10 Furthermore, 3 main coronary vessels (the left anterior descending, circumflex, and right coronary) (Figure 3) should probably be termed arteries, but the most distal vessels should be called coronary branches. We have proposed that a common proximal trunk, which joins 2 or 3 coronary arteries, should be named a mixed trunk. The only normally observed mixed trunk is the left main (common trunk or stem).10

The following criteria are proposed to define each coronary artery:

1. The right coronary artery (RCA) is the vessel that provides blood flow to the right ventricular free wall. It is not essential for the posterior descending branch to originate from the RCA (the most common pattern) or that the ostium of the RCA be located at the right anterior sinus of Valsalva (which is normal).

2. The left anterior descending artery is the vessel that provides blood flow to the anterior interventricular septum. It is not essential for the diagonal branch to originate from this vessel (as is normal).

3. The circumflex artery is the vessel that provides blood flow to the free wall of the left ventricle, on the obtuse margin of the heart.10

Incidence of Coronary Artery Anomalies
Curiously, the literature shows that the overall incidence of CAAs is consistently mentioned by most authors, even the hundreds of them who report individual cases. This practice has led the nonspecialized audience to assume that CAAs, as a whole, are a serious threat (not simply that some rare individual forms may be so).10 The greatest confusion in this regard is about myocardial bridges: Are they an anomaly, a pathological anomaly, or simply a normal feature of some coronary arteries in humans? The fact that such bridges are surely present in >1% of the general population suggests that they may be a normal variant.10,17 Should only “severe” myocardial bridges be counted as pathological anomalies, and, if so, by what criteria?10

In one of the few prospective analyses to involve strict diagnostic criteria, which was performed in a continuous series of 1950 patients studied by coronary angiography, our group found that CAAs had a global incidence of 5.64% (Table 3), which is much higher than usually reported. Particularly noteworthy were the 0.92% incidence of anomalous origination of the RCA from the left sinus and the 0.15% incidence of anomalous origination of the left coronary artery from the right sinus (for a total incidence of 1.07% for ACAOS).10

TABLE 1. Normal Features of the Coronary Anatomy in Humans

<table>
<thead>
<tr>
<th>Feature</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ostia</td>
<td>2 to 4</td>
</tr>
<tr>
<td>Location</td>
<td>right and left anterior sinuses (upper midsection)</td>
</tr>
<tr>
<td>Proximal orientation</td>
<td>45° to 90° off the aortic wall</td>
</tr>
<tr>
<td>Proximal common stem or trunk</td>
<td>only left (LAD and Cx)</td>
</tr>
<tr>
<td>Proximal course</td>
<td>direct, from ostium to destination</td>
</tr>
<tr>
<td>Mid-course</td>
<td>extramural (subepicardial)</td>
</tr>
<tr>
<td>Branches</td>
<td>adequate for the dependent myocardium</td>
</tr>
<tr>
<td>Essential territories</td>
<td>RCA (RV free wall), LAD (anteroseptal), OM (LV free wall)</td>
</tr>
<tr>
<td>Termination</td>
<td>capillary bed</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery; RV, right ventricular; OM, obtuse marginal artery; and LV, left ventricular.

Figure 1. Angiograms from a 52-year-old man, in the left anterior oblique cranial (A) and right anterior oblique (B) projections. The patient had atypical chest pain and borderline nuclear stress test results. In these views, the whole coronary system is visualized from a single ostium, located at the right sinus. The right coronary artery (RCA) splits off from a short common trunk (CT), and continues into a terminal obtuse marginal branch (OM). The left main trunk (LM) crosses to the left off the CT, and courses intraseptally to give off a large septal branch (SB). The left coronary artery ends in the left anterior descending (LAD) and ramus (RM) branches. This is a case of clinically benign single coronary artery, which should more properly be called single coronary ostium because all the coronary arteries are present, though they are anomalous in their origin and course.
A group at the American Armed Forces Institute of Pathology recently reported some notable and groundbreaking statistics. In a continuous series of 6.3 million 18-year-old recruits who underwent intense military training for 8 weeks, the researchers identified 277 deaths unrelated to trauma. A review of the clinical and necropsy charts showed that, of 64 cardiac deaths, 21 (33%) were related to ACAOS.

TABLE 2. Classification of Coronary Anomalies in Human Hearts

<table>
<thead>
<tr>
<th>A. Anomalies of origination and course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Absent left main trunk (split origination of LCA)</td>
</tr>
<tr>
<td>2. Anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (for each artery)</td>
</tr>
<tr>
<td>a. High</td>
</tr>
<tr>
<td>b. Low</td>
</tr>
<tr>
<td>c. Commissural</td>
</tr>
<tr>
<td>3. Anomalous location of coronary ostium outside normal &quot;coronary&quot; aortic sinuses</td>
</tr>
<tr>
<td>a. Right posterior aortic sinus</td>
</tr>
<tr>
<td>b. Ascending aorta</td>
</tr>
<tr>
<td>c. Left ventricle</td>
</tr>
<tr>
<td>d. Right ventricle</td>
</tr>
<tr>
<td>e. Pulmonary artery</td>
</tr>
<tr>
<td>(1) LCA that arises from posterior facing sinus</td>
</tr>
<tr>
<td>(2) Cx that arises from posterior facing sinus</td>
</tr>
<tr>
<td>(3) LAD that arises from posterior facing sinus</td>
</tr>
<tr>
<td>(4) RCA that arises from anterior right facing sinus</td>
</tr>
<tr>
<td>(5) Ectopic location (outside facing sinuses) of any coronary artery from pulmonary artery</td>
</tr>
<tr>
<td>(a) From anterior left sinus</td>
</tr>
<tr>
<td>(b) From pulmonary trunk</td>
</tr>
<tr>
<td>(c) From pulmonary branch</td>
</tr>
<tr>
<td>f. Aortic arch</td>
</tr>
<tr>
<td>g. Innominate artery</td>
</tr>
<tr>
<td>h. Right carotid artery</td>
</tr>
<tr>
<td>i. Internal mammary artery</td>
</tr>
<tr>
<td>j. Bronchial artery</td>
</tr>
<tr>
<td>k. Subclavian artery</td>
</tr>
<tr>
<td>l. Descending thoracic aorta</td>
</tr>
<tr>
<td>4. Anomalous location of coronary ostium at improper sinus (which may involve joint origination or “single” coronary pattern)</td>
</tr>
<tr>
<td>a. RCA that arises from left anterior sinus, with anomalous course</td>
</tr>
<tr>
<td>(1) Posterior atrioventricular groove or retrocardiac</td>
</tr>
<tr>
<td>(2) Retroaortic</td>
</tr>
<tr>
<td>(3) Between aorta and pulmonary artery (intramural)</td>
</tr>
<tr>
<td>(4) Intraseptal</td>
</tr>
<tr>
<td>(5) Anterior to pulmonary outflow</td>
</tr>
<tr>
<td>(6) Posteroanterior interventricular groove (wraparound)</td>
</tr>
<tr>
<td>b. LAD that arises from right anterior sinus, with anomalous course</td>
</tr>
<tr>
<td>(1) Between aorta and pulmonary artery (intramural)</td>
</tr>
<tr>
<td>(2) Intraseptal</td>
</tr>
<tr>
<td>(3) Anterior to pulmonary outflow</td>
</tr>
<tr>
<td>(4) Posteroanterior interventricular groove (wraparound)</td>
</tr>
<tr>
<td>c. Cx that arises from right anterior sinus, with anomalous course</td>
</tr>
<tr>
<td>(1) Posterior atrioventricular groove</td>
</tr>
<tr>
<td>(2) Retroaortic</td>
</tr>
<tr>
<td>d. LCA that arises from right anterior sinus, with anomalous course</td>
</tr>
</tbody>
</table>

Continued

| (1) Posterior atrioventricular groove |
| (2) Retroaortic |
| (3) Between aorta and pulmonary artery |
| (4) Intraseptal |
| (5) Anterior to pulmonary outflow |
| (6) Posteroanterior interventricular groove |
| 5. Single coronary artery (see A4) |
| B. Anomalies of intrinsic coronary arterial anatomy |
| 1. Congenital ostial stenosis or atresia (LCA, LAD, RCA, Cx) |
| 2. Coronary ostial dimple |
| 3. Coronary ectasia or aneurysm |
| 4. Absent coronary artery |
| 5. Coronary hypoplasia |
| 6. Intramural coronary artery (muscular bridge) |
| 7. Subendocardial coronary course |
| 8. Coronary crossing |
| 9. Anomalous origination of posterior descending artery from the anterior descending branch or a septal penetrating branch |
| 10. Split RCA |
| a. Proximal+distal PDs that both arise from RCA |
| b. Proximal PD that arises from RCA, distal PD that arises from LAD |
| c. Parallel PDs ×2 (arising from RCA, Cx) or “codominant” |
| 11. Split LAD |
| a. LAD+first large septal branch |
| b. LAD, double (parallel LADs) |
| 12. Ectopic origination of first septal branch |
| a. RCA |
| b. Right sinus |
| c. Diagonal |
| d. Ramus |
| e. Cx |
| C. Anomalies of coronary termination |
| 1. Inadequate arteriolar/capillary ramifications |
| 2. Fistulas from RCA, LCA, or infundibular artery to: |
| a. Right ventricle |
| b. Right atrium |
| c. Coronary sinus |
| d. Superior vena cava |
| e. Pulmonary artery |
| f. Pulmonary vein |
| g. Left atrium |
| h. Left ventricle |
| i. Multiple, right + left ventricles |
| D. Anomalous anastomotic vessels |

LCA indicates left coronary artery; LAD, left descending coronary artery; RCA, right coronary artery; Cx indicates circumflex; and PD, posterior descending branch. Adapted from Angelini P et al with permission from Lippincott, Williams & Wilkins. Copyright 1999.

18-year-old recruits who underwent intense military training for 8 weeks, the researchers identified 277 deaths unrelated to trauma. A review of the clinical and necropsy charts showed that, of 64 cardiac deaths, 21 (33%) were related to ACAOS.
of the left coronary artery (left-ACAOS) and that no other CAAs resulted in cardiac death. Although the authors did not specify, it is likely that none of these cases of left-ACAOS had been diagnosed before death (in an environment in which medical evaluations are routine). This is the first large-scale study of CAAs in which the denominator (all candidates at risk) was known, the setting of the clinical events was consistent (extreme physical training), and all the fatal events led to necropsy studies.18

In comparison, Drory and colleagues19 studied the incidence of CAAs in a continuous series of 162 patients with sudden unexpected death. The patients were >40 years of age and underwent routine autopsy studies in Israel, where an autopsy is obligatory in such cases. The incidence of CAA-related sudden death was 0.6% (1 of 162 cases); taken together with the recent military recruit series,18 this result suggests that extreme exercise plays a powerful role in such deaths.

In conclusion, the main interest of current clinical investigators seems to be to establish the incidence of those individual types of CAAs that have become recognized for their clinical consequences.

Pathophysiological Mechanisms and Clinical End Points
To understand the clinical impact of CAAs, the fundamental challenge is to firmly establish, for a particular type of CAA, a mechanism capable of interference with the coronary artery’s function to provide adequate blood flow to the dependent myocardium. Table 4 summarizes such mechanisms and the conditions under which they apply.10 Whereas some CAAs may cause occasional ischemia, others (eg, anomalous origination of the left coronary artery from the pulmonary artery) obligatorily cause ischemia, and yet others only predispose the patient to have a misdiagnosis or complications (clotting, spasm, or atherosclerotic buildup).

The present review is limited to only 1 kind of coronary anomaly, ACAOS, which has recently been recognized as having serious prognostic implications in young individuals.5–7,9,12,20 In cases of ectopic origination of a CAA, only 1
FIGURE 3. Conceptual diagram that shows most of the possible paths (1 through 5) by which the RCA, left anterior descending artery (LAD), and circumflex artery (Cx) can potentially connect with the opposite coronary cusps. Paths: 1, Retrocardiac; 2, retroaortic; 3, preaortic, or between the aorta and pulmonary artery; 4, intraseptal (supracristal); 5, prepulmonary (precardiac). The aortic and pulmonary cusps are labeled according to their position in space: AL indicates antero-left; AR, antero-right; P, posterior; M, mitral valve; and T, tricuspid valve. Reproduced from Angelini et al10 with permission from Lippincott Williams & Wilkins. Copyright 1999.

specific abnormal course, traditionally called interarterial, or “between the aorta and pulmonary artery,” is associated with a severe prognosis.20–25 Indeed, that anomaly has recently been observed, on intravascular ultrasound (IVUS) imaging, to consist of intramural proximal intussusception of the ectopic artery at the aortic-root wall.26 Never has an extramural course been observed with IVUS in such a scenario.21,25,27,28 The traditional terminology (between the aorta and pulmonary artery) implied that the aberrant artery was liable to a scissors-like mechanism, created by the close proximity of the aorta and pulmonary artery, especially during exer-
tion.23 Such a mechanism is unlikely, however, because at the site of closest aortopulmonary proximity the anomalous artery lies inside the aortic wall.26 In our more recent extensive experience with IVUS examination of CAAs, we have occasionally found an intramural aortic course in some type of ACAOS without an interarterial course. Specifically, only 2 patients had an unusual intramural anomalous “ret-
roaortic” course: In 1 case, the left coronary arose from the posterior sinus27; in the other case, the circumflex artery arose from the right sinus.

The reasons for our insistence on the intussusception of anomalous arteries are related to the following newly discovered mechanisms of stenosis (Figure 4):

1. Coronary hypoplasia. Our group has discovered that the intramural intussuscepted segment of the proximal ectopic artery is smaller in circumference than the more distal extramural vessel. With IVUS, we found it valuable to quantify this parameter with the hypoplasia index (ie, the ratio of the circumference of the intramural segment with respect to the circumference of the more distal segment).26,27 Arteries that arise congenitally inside the aortic media likely cannot grow normally either before or after birth.

2. Lateral compression. The cross section of the intramural segment is characteristically not circular but ovoid (Figure 4). The lateral compression results in a smaller area than that possessed by a circle of the same circumference.17 This parameter can be quantified with the asymmetry ratio (the ratio of the smallest to the largest diameter in an IVUS cross section).27 Additionally, our group has observed that the smaller diameter is further compressed during each systole, as manifested by pulsatile behavior observed with IVUS during the cardiac cycle. This liability to undergo intermittent worsening is most likely related to changes in stroke volume (and pulsatility of the ascending aorta) and to tachycardia, which is a behavior that becomes manifest during IVUS imaging when an experimental pharmacolog-
ical challenge simulates exercise conditions.26 For in-
stance, in 3 symptomatic patients with left-ACAOS, we found 49% to 70% area stenosis at baseline, which in-
creased by 8% to 10% with stimulation.27 Such lesions are in the range of what the Coronary Artery Surgery Study (CASS) defined as critical stenosis of the left main coro-
mary, which can cause sudden death.28 In this context, it is important to recognize the hemodynamic changes that occur during sports activities that involve maximal exer-
tion; for example, from the resting state, the heart rate increases from 65 to 180 bpm, the cardiac output from 5 to 22 L/min, and the stroke volume from 77 to 122 cc.29

3. Stenotic segment length. With any coronary stenosis, the segmental length is another measure of severity. In ACAOS that involves the RCA, as well as in left-ACAOS, the length of the stenosis varies between 5 and 15 mm.26,27

In our series, all 3 of the aforementioned parameters showed great individual variability. It is likely that aortic wall distensibility (degree of cross-sectional area enlargement associated with a certain increase in pressure) is a further related variable that depends on intrinsic anatomic changes in the aortic wall (as in medial cystic necrosis or aortic dissec-
tion), changes in the aortic pressure (as at the onset of hypertension or aortic regurgitation), or a rapid weight gain, especially in patients who receive negative chronotropic agents, which increase the stroke volume if the cardiac output remains essentially unchanged. Moreover, a treadmill stress test, which should be transformed into an adenosine test because of an inadequate effort or chronotropic response, may be the most accurate predictive test for ACAOS because it associates an increased cardiac output with nonphysiological bradycardia. Unfortunately, though, such a hybrid protocol is a potential cause of sudden death, specifically in ACAOS carriers, and should generally be avoided or at least closely monitored in a hospital environment.

When a carrier of ACAOS dies suddenly, in the absence of other lethal cardiovascular conditions, a low cardiac output and bradycardia or asystole typically occur early after extreme exercise, after which syncope and/or death ensues. Terminal ventricular fibrillation may also occur as a manifestation of critical ischemia or of reperfusion arrhythmia. 

Both the anomalous right and left coronary arteries can be responsible for sudden death, although the risk has not been adequately quantified in specific studies. Most likely, predisposing factors include the severity of baseline stenosis, the specific conditions at the time of the crisis, and the myocardial territory at risk. Additionally, one must realize that the possible manifestations of ACAOS include not only sudden death but also dyspnea, palpitations, angina pectoris, dizziness, and syncope. Whereas sudden death is usually associated with extreme exercise in young adults, the other manifestations of ACAOS are more frequently seen in older adults (in our experience, specifically women) and are related to the onset of hypertension. Interestingly, Cheitlin claimed that sudden death is seen only in young patients, possibly because of progressive hardening of the aortic wall in adults.

During aortic valve replacement, an intramural ectopic coronary artery can also be liable to critical worsening of extrinsic compression by the prosthetic ring, as recently reviewed by Morimoto and colleagues.

### Table 4. Pathophysiological Mechanisms and Coronary Anomalies (Functional Classification)

<table>
<thead>
<tr>
<th>Pathophysiological Mechanism</th>
<th>Coronary Anomaly</th>
<th>Proof of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misdiagnosis</td>
<td>“Missing” coronary artery</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>“Hypoplastic” coronary artery</td>
<td>x</td>
</tr>
<tr>
<td>Myocardial ischemia, primary (fixed and/or episodic)</td>
<td>Ostial atresia</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Ostial stenosis</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>ALCAPA</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Muscular bridge</td>
<td>x</td>
</tr>
<tr>
<td>Myocardial ischemia, secondary (episodic)</td>
<td>Tangential origin (ACAOS) intramural course</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Myocardial bridge, plus spasm and/or clot</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary ectasia (plus mural clot)</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary fistula (plus mural clot)</td>
<td>x</td>
</tr>
<tr>
<td>Increased risk of fixed coronary atherosclerotic disease</td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>ALCAPA</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary ectasia</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Muscular bridge (proximal to)</td>
<td>x</td>
</tr>
<tr>
<td>Secondary aortic valve disease</td>
<td>Coronary aneurysm (ostial)</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>ALCAPA</td>
<td>x</td>
</tr>
<tr>
<td>Increased risk of bacterial endocarditis</td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (hibernation)</td>
<td>ALCAPA</td>
<td>x</td>
</tr>
<tr>
<td>Volume overload</td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>ALCAPA</td>
<td>x</td>
</tr>
<tr>
<td>Unusual technical difficulties during coronary angiography or angioplasty</td>
<td>Ectopic ostia (tangential)</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Split left coronary artery</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Coronary fistula</td>
<td>x</td>
</tr>
<tr>
<td>Complications during cardiac surgery</td>
<td>Ectopic ostia and proximal course</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Muscular bridge</td>
<td>x</td>
</tr>
</tbody>
</table>

ALCAPA indicates anomalous origination of the left coronary artery from the pulmonary artery. Adapted from Angelini P et al with permission from Lippincott, Williams & Wilkins. Copyright 1999.
Outlines for Diagnostic and Treatment Protocols

In carriers of ACAOS, the clinical histories are consistent in only 1 aspect: Either these patients die suddenly (typically at a young age and after extreme exertion), or they have no characteristic presentation. Most patients are asymptomatic for a large portion of their lives, and an atypical chest-pain syndrome is the most common reason they are referred for coronary angiography, which is when the diagnosis is typically made. The milder cases are more likely to be identified fortuitously (because of a falsely positive stress test and/or coincidental atherosclerotic disease).

The fact that CAAs include many different entities and that no single observer or group has collected a large enough series to clarify the natural prognosis of each entity may contribute to our difficulty in the clinical identification of these lesions, especially the ones that could lead to angina or sudden cardiac death. For most types of coronary anomalies, the fundamental clinical approach could be: “Do not bother to look for these innocent anomalies, but be prepared to recognize them as benign if one is accidentally found, typically at coronary angiography.” However, for a few CAAs that are possibly or predictably malignant (fundamentally, ACAOS), we should establish solid diagnostic screening protocols, especially for athletes and other young individuals subjected to extreme exertion. As noted above, ACAOS patients can succumb to sudden cardiac death, usually but not necessarily at a young age, possibly even at the newborn stage.

Retrospectively reviewed, only a few persons reported to have died of ACAOS had significant symptoms, usually atypical chest pain, dyspnea, syncope, or their equivalents, before the final event. A specific workup protocol is indicated mostly for athletes and military personnel with these symptoms. In view of the fairly rare nature of ACAOS, it would not seem practical or cost-effective to extend the indications for such a workup to all schoolchildren on a routine basis. Nevertheless, larger prospective studies are needed before this decision can become final.

In patients with suspected ACAOS, testing should sequentially include electrocardiography, Holter monitoring, (basi-
cally to document atrial or ventricular arrhythmias as non-
specific markers of ACAOS), and focused expert
echocardiography (transthoracic and, if needed, transesopha-
geal) with Doppler interrogation to identify the coronary
origin and proximal course.\textsuperscript{40–42} In particular, the reported
0.17\% incidence of ACAOS found by examination of a series
of 2388 routine echocardiograms\textsuperscript{40} must be compared with
the 1.07\% incidence found at coronary angiography.\textsuperscript{10} The
implication is that echocardiography is probably not as
reliable a means to diagnose this disorder (especially if
performed in adults and without specifically looking for
ACAOS). The authors of the echocardiographic study\textsuperscript{37}
reported that 1 of their negative results was followed by
sudden death during follow-up observation, the diagnosis of
ACAOS becoming apparent only at autopsy.

If at least 2 normally located coronary ostia are identified
with echocardiography, which is more often possible in
children than adults, no further workup for ACAOS is
probably required. If the coronary ostia are not clearly
identified echocardiographically, however, or if an alternative
method is needed, computed tomography or magnetic reso-
nance imaging is recommended.\textsuperscript{21,41,43} These methods not
only identify ACAOS more reliably than echocardiography,
but also allow description of the dependent territory,\textsuperscript{21} which
 correlates with the prognosis, as discussed above. When
ACAOS is identified in this manner, a further workup should
include nuclear stress testing. Although the result is usually
negative, this method is important both to evaluate effort-
induced ischemia and scars and to establish a baseline for
follow-up assessment in case of eventual intervention.
Furthermore, selective coronary angiography is indicated more to
rule out additional obstructive coronary disease of atheroscle-
rotic origin than to evaluate the severity of congenital
obstruction at the proximal ectopic vessel. The need for
interventional treatment can be substantiated only by IVUS,
as discussed above.\textsuperscript{26,27}

\textbf{Treatment Options}

Symptomatic carriers of ACAOS have 3 treatment options:
medical treatment/observation, coronary angioplasty with
stent deployment, and surgical repair. Despite the limitations
of our current knowledge of such anomalies, intervention
may be justified in some cases to prevent sudden death and
improve the quality of life. Medical treatment (essentially
with \(\beta\)-blockers) is probably as effective as restriction of
activity (avoidance of severe exertion) in these patients.\textsuperscript{39}

In a significant number of cases, right-ACAOS may not
warrant intervention. Precise IVUS/clinical correlations
should be prospectively obtained to establish acceptable
selection criteria. Stent-angioplasty of the obstructed prox-
imal intramural segment of a patient with right-ACAOS is
technically feasible,\textsuperscript{26,44} and is probably justifiable in the
presence of (1) disabling symptoms and/or a high risk of
sudden death, (2) area stenosis more severe than 50\% with
respect to the distal normal vessel on IVUS, (3) a large
dependent myocardial territory (more than a third of the
total), and (4) reversible ischemia, as documented by a
nuclear stress test.

Besides indicating the need for intervention, IVUS is also
essential for proper deployment of a stent. We use IVUS data
both to measure the length of the obstructed intramural RCA
and to evaluate the cross-sectional area after stent deploy-
ment, aiming for a target luminal area similar to that of the
distal vessel. Initially, timid dilatation of stents (for fear of
aortic-wall dissection if excessively large balloon sizes were
used) resulted in incomplete apposition along the longest
diameter, some residual stenosis, and sometimes early post-
operative restenosis. Presently, we feel confident that the
immediate and late results are improved if full luminal
restoration, to match the area of the distal vessel, is attained
at the intramural segment and for about 4 mm beyond it.

Apparently, only 1 group, in China, has reported the use of
stent-angioplasty for left-ACAOS.\textsuperscript{45} In this case, the patient
was a 14-year-old child with severe symptoms who received
a stent at the left main trunk. The early results were favorable,
but we prefer to postpone such experimental use of stents
until stent-angioplasty is well established for the lower-risk
indication of right-ACAOS.

Our initial experience suggests that drug-eluting stents
offer the best probability to avoid restenosis, but definitive
data need to be collected regarding this off-label use of stents.
Moreover, restenosis appears to be rare, and, if it does occur,
is related to in-stent fibrocellular growth, not stent compres-
sion. Like many others, however, our group considers that
left-ACAOS is generically, in itself, a solid indication for
surgical intervention.\textsuperscript{27} Nevertheless, we continue to acquire
IVUS data in these patients to further refine our treatment
protocols. Despite the absence of objective studies, surgical
treatment of ACAOS has been performed in large series of
patients for several years.\textsuperscript{43,46} Surgical correction, which is
especially recommended for left-ACAOS that involves a
large territory at risk, may consist of (1) direct reimplantation
of the ectopic artery at the aortic root (a technically difficult
and unreliable approach); (2) unroofing of the intramural
coronary segment, from the ostium to the exit point, off the
aortic wall; or (3) osteoplasty, which creates a new ostium at
the end of the ectopic artery’s intramural segment (Figure
5).\textsuperscript{27,43,46–48}

Athletes and military personnel known to be ACAOS
carriers should be advised by a specially trained cardiologist
about permitted versus prohibited physical activities before
and after intervention. Current guidelines issued by profes-
sional associations state that untreated carriers of ACAOS
should not be involved in competitive sports or other stren-
uous activities.\textsuperscript{39} Treated patients should be reevaluated
before being allowed to resume exercise at maximal capacity.

\textbf{Conclusions}

Coronary artery anomalies should be regarded as an uneven
diverse group of congenital disorders whose manifestations
and pathophysiological mechanisms are highly variable. To
be competent to advise CAA carriers, especially in the
context of sporting or military activities, cardiologists should
undergo specific training in these disorders. IVUS is the
preferred means to evaluate the mechanisms responsible for
ischemia in potentially significant CAAs, especially ACAOS.
Dr Paolo Angelini is an occasional expert witness in cases of
Virginia Fairchild, Senior Medical Editor, Texas Heart Institute at St.

Clearly, this aspect of cardiology will not be able to
develop fully without extensive collaboration between indi-
vidual cardiologists and institutions. To further this goal,
the Texas Heart Institute has established a Web site designed
to promote multicenter collaboration on protocols dedicated to
ACAOS patients (http://texasheart.org/Education/Resources/
caac.cfm). Only such efforts can give rise to the large-scale
studies needed to define the prognosis and optimal treatment
of individual forms of CAA.

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References
1. Roberts WC. Major anomalies of coronary arterial origin seen in
TJ, McNamara DG, eds. The Science and Practice of Pediatric Cardi-
3. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with
20:640–647.
JK, ed. The Clinical Recognition of Congenital Heart Disease, 4th ed.
5. Libertothon RR. Sudden death from cardiac causes in children and young
6. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO.
Sudden death in young competitive athletes: clinical, demographic, and
7. Taylor AJ, Byers JP, Cheitlin MD, Virmani R. Anomalous right or left
coronary artery from the contralateral coronary sinus: “high-risk” abnor-
malities in the initial coronary artery course and heterogeneous clinical
8. Virmani R, Rogen K, Cheitlin MD. Congenital coronary artery anom-
alies: pathologic aspects. In: Virmani R, Forman MB, eds. Nonathero-
sclerotic Ischemic Heart Disease. New York: Raven Press; 1989:
153–183.
coronary artery anomalies with origin from the wrong aortic sinus leading
to sudden death in young competitive athletes. J Am Coll Cardiol.
10. Angelini P, Villason S, Chan AV, Dzie JG. Normal and anomalous
coronary arteries in humans. In: Angelini P, ed. Coronary Artery Anom-
alies: A Comprehensive Approach. Philadelphia: Lippincott Williams &
Wilkins; 1999:27–150.
Anderson RH, eds. Pathology of Congenital Heart Disease. London:
12. Libertothon RR, Dinmore RE, Fallon JT. Aberrant coronary artery origin
from the aorta: report of 18 patients, review of literature and delineation
13. Virmani R, Chun PK, Goldstein RE, Robinowitz M, McAllister HA.
Acute takeoffs of the coronary arteries along the aortic wall and con-
genital coronary ostial valve-like ridges: association with sudden death.
14. Barth CW 3rd, Roberts WC. Left main coronary artery originating from
the right sinus of Valsalva and coursing between the aorta and pulmonary
artery disease and sudden death in the young. Br Heart J. 1992;68:
601–607.
16. Willerson JT. Coronary artery anomalies: more work is needed. In:
17. Angelini P, Trivelatto M, Donis J, Leachman RD. Myocardial bridges: a
18. Eckart RE, Scoville SL, Campbell CL, Shry EA, Stajduhar KC, Potter
RN, Pearse LA, Virmani R. Sudden death in young adults: a 25-year
review of autopsies in military recruits. Ann Intern Med. 2004;141:
829–834.
Sudden unexpected death in persons less than 40 years of age. Am J Cardiol.
20. Roberts WC, Kragel AH. Anomalous origin of either the right or left main
 coronary artery from the aorta without coursing of the anomalistically
arising artery between aorta and pulmonary trunk. Am J Cardiol.
21. Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, patho-
22. Grollman JH Jr, Mao SS, Weinstein SR. Arteriographic demonstration of
both kinking at the origin and compression between the great vessels of
an anomalous right coronary artery arising in common with a left
 coronary artery from above the left sinus of Valsalva. Cathet Cardiovasc
23. Cheitlin MD, De Castro CM, McAllister HA. Sudden death as a compli-
cation of anomalous left coronary origin from the anterior sinus of
Valsalva, a not-so-minor congenital anomaly. Circulation. 1974;50:
780–787.
24. Frescura C, Basso C, Thiene G, Corrado D, Pennelli T, Angelini A,
Daliento L. Anomalous origin of coronary arteries and risk of sudden
death: a study based on an autopsy population of congenital heart disease.
Hum Pathol. 1998;29:689–695.
25. Roberts WC, Shirani J. The four subtypes of anomalous origin of the left
main coronary artery from the right aortic sinus (or from the right
artery arising from the opposite sinus: descriptive features and patho-
physiologic mechanisms, as documented by intravascular ultra-
27. Angelini P, Walmsley RP, Liberrosi A, Ott DA. Symptomatic anomalous
origination of left coronary artery from the opposite sinus of vlsalva:
clinical presentations, diagnosis, and surgical repair. Tex Heart Inst J.
2006;33:171–179.
28. Coronary artery surgery study (CASS): a randomized trial of coronary
29. Mitchell JH, Haskell W, Smell P, Van Camp SP, Task Force 8; classifi-
30. Cox ID, Bunce N, Fluck DS. Failed sudden cardiac death in a patient with
an anomalous origin of the right coronary artery. Circulation. 2000;102:
1461–1462.
31. Saeed M, Gabara R, Strasberg B, Kusniec J, Rosanio S, Ware DL,
Birnbaun Y. Reperfusion-related polymorphic ventricular tachycardia as

Figure 5. Diagram representation of a case of single coronary
ostium at the right sinus. The LM runs intramurally inside the
aortic-wall left sinus, just below the anterior aortic commissure,
and takes off from the aorta at the center of the left cusp. At
this point, a circle with stitches represents the newly created
ostium after surgical repair. Cx indicates circumflex. Repro-
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44. Harirhan R, Kacere RD, Angelini P. Can stent-angioplasty be a valid alternative to surgery when revascularization is indicated for anomalous origination of a coronary artery from the opposite sinus? Tex Heart Inst J. 2002;29:308–313.
Coronary Artery Anomalies: An Entity in Search of an Identity
Paolo Angelini

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