Novel Imaging of Coronary Artery Anomalies to Assess Their Prevalence, the Causes of Clinical Symptoms, and the Risk of Sudden Cardiac Death

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In a fundamental 1974 article, Cheitlin et al[1] of the Armed Forces Institute of Pathology emphasized the special role of anomalous aortic origin of the coronary arteries and differentiated this condition from the other coronary artery anomalies (CAAs) as being associated with an increased frequency of sudden cardiac death (SCD) in young persons, especially during strenuous exertion. More recently, CAAs have also been considered possible causes of clinically disabling symptoms, including dyspnea, angina pectoris, and syncope, especially in young adults.[2–5] Clinicians and epidemiologists have identified the need to prevent not only SCD in young persons, especially athletes or military recruits, but also other CAA-related symptoms in persons of any age.[6–12] Much of the available information concerning the incidence of SCD in carriers of CAAs is lacking a denominator (measure of the carriers at risk). The most notable study of SCD incidence is a classic 2004 article by Eckart et al,[7] who reported the mortality rate (>25 years) that US military recruits experienced during a 2-month-long boot-camp training period. All the recruits were involved in strenuous exercise and had undergone routine screening based on a history and physical examination performed by general practitioners. Of the 23 million recruits, 64 died of SCD (0.28 per 100 000 per 2 months, or 1.68 per 100 000 per year). Of these deaths, 21 (33%) were attributed to CAAs, specifically anomalous origin of the left coronary artery from the right sinus of Valsalva with an interarterial course.

To establish a solid theory and a preventive policy in this field, we must understand the pathophysiology of CAAs, identify the prevalence of individuals living with different kinds of CAAs (the denominator), clarify the individual severity of each case, study the influence of different types of exertion, and identify the incidence of SCD in a general population or a specific subpopulation. Finally, we need to establish effective and rational treatment strategies.[4,8,10,12–18] This review briefly summarizes our current knowledge (or lack of it) concerning (1) the nature of CAAs (pathophysiology, as centered on the intramural course and stenosis), (2) the prevalence of CAAs in the population (the role of cardiac magnetic resonance imaging [MRI] for screening), and (3) the significance of symptoms and stress testing, as correlated with the severity of stenosis (the central role of intravascular ultrasonography [IVUS]). It also discusses new treatment options that can be supported by current imaging and clinical evaluation methods.

Anomalous Coronary Artery Arising From the Opposite Sinus Is a Special CAA

As Eckart et al's[7] report also suggests, evidence from autopsy series indicates that anomalous origin of the left coronary artery from the opposite side of the aorta is associated with SCD in 57% of cases involving left anomalous coronary artery arising from the opposite sinus (L-ACAOS) and in 25% of cases involving right ACAOS (R-ACAOS; Figures 1–3).[17] The causal mechanism of SCD was initially considered to be related to either hypoplasia of the culprit coronary artery, bending or kinking of the proximal coronary ectopic segment (tangentially exiting the aorta), an acute angle and a slit-like or flap-like closure of the orifice, or a coronary course between the aorta and pulmonary artery, resulting in scissors-like compression.[1,4,5,13,14,16–18] Attempts to quantify the severity of the ischemic effect of ACAOS in individual cases were pursued, but they were initially unsuccessful in autopsy series.[17]

To fully appreciate the importance of ACAOS, the prevalence of these anomalies in the population under study[18] needs to be identified; this need was not clearly recognized until recently.[13,19] The initial popularization of coronary angiography from the 1970s into the 1990s[5] led to extensive but inconsistent reports about the prevalence of CAAs. These reports were limited because they essentially concerned patients observed in the catheterization laboratory, who were evaluated without strict diagnostic criteria; also, these patients were preselected, because they were mostly referred for diagnostic work-up for signs or symptoms of myocardial ischemia.[2,3] The more recent widespread use of coronary computerized tomographic angiography (CTA), generally performed in adults with a variable pretest probability of coronary artery disease, further challenged clinicians' ability to reliably evaluate the prevalence and importance of CAAs in the general population.[9,10] Only recent novel attempts at screening the general
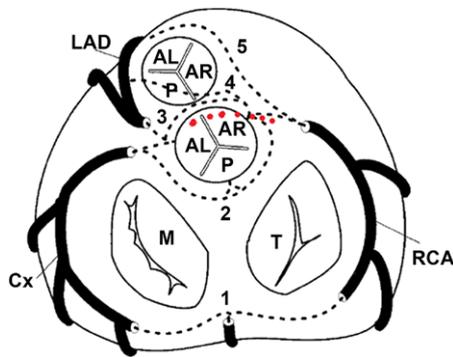
Figure 1. Diagrammatic conceptual representation of the spectrum of ectopic aortic origin and courses of the coronary arteries in a coronal plane of the base of the heart. Each of the 3 elementary coronary arteries (right coronary artery [RCA], left anterior descending artery [LAD], and circumflex artery [Cx]) can originate off the aortic root from abnormal sites, implying different proximal coronary courses. Course 3 is the preaortic course (intramural, anomalous coronary artery arising from the opposite sinus [ACAOS]), which carries the highest risk of ischemic clinical events because of stenosis (see text). Course 1 is prepulmonic (epicardial), 2 is intraseptal (inside the ventricular septum), 4 is retroaortic (behind the aortic root, inside the central fibrous body, and in front of the left atrial wall), and 5 is retrocardiac (at the posterior atrioventricular sulcus). AL indicates anterior-left; AR, anterior-right; M, mitral; P, posterior aortic sinuses; and T, tricuspid. Modified from Angelini et al[2] with permission of the publisher. Copyright © 1999, Lippincott Williams & Wilkins. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

population with echocardiography or magnetic resonance angiography (MRA) have finally established the conditions for improving our knowledge of the denominator in the risk fraction (the number of cases of SCD divided by the number of persons with CAAs in the general population rather than only in autopsy series).[15,19–22] Definitive data about CAA-associated mortality are still lacking, because of a lack of studies based on defined and controlled populations.[13]

This report attempts to clarify this matter by presenting an overview of more recent and precise approaches to CAA screening, pathophysiology, and clinical evaluation.

Systematic Screening for CAAs

Because CAAs are potential causes of severe clinical events in young persons and cannot be identified on the basis of a history and physical examination, various imaging modalities are being tested for their detection.

Magnetic Resonance Imaging

At our Center for Coronary Artery Anomalies, recent MRA-based screening of a continuous preliminary series of 1836 students (aged between 11 and 15 years) has finally presented credible data regarding the prevalence of ACAOS. These data are essential for discovering the risk of SCD. Our method is precise, extensive, and related to a general population (the denominator).[19] It involves the use of an Achieva 1.5 T A-Series scanner with 32-channel coils (Philips, Amsterdam, the Netherlands) in a mobile unit that has been visiting several public middle schools in Houston. In this ongoing study, we do not use any sedation, contrast medium, or medication.

We routinely acquire standard 2-chamber, 4-chamber, and left ventricular outflow tract gradient echo steady-state free precession cine images, followed by a stack of short-axis cine images from the left ventricle, with in-plane resolution of 1.8×1.8 mm and an 8-mm slice with a 2-mm gap for 30 cardiac phases. Coronary MRA images are obtained with a 3-dimensional steady-state free precession electrocardiography-gated echo-navigator sequence with T2 prepreparation. The aortic root and the left ventricular outflow tract are included to ensure identification of the coronary ostia and proximal segments. Acquisition takes a total of 15 to 25 minutes, making this method a much simplified version of cardiac MRI.

One foundational finding of this study has been that CAAs are the most frequent high-risk cardiovascular condition for SCD in young persons: indeed, 40% of young people with a high-risk cardiovascular condition have a CAA.[19] Our basic plan was to screen ≈10 000 children for only the types of CAAs capable of causing ischemia and SCD.[13,19] The term ACAOS was refined to include only unusual coronary patterns involving an anomalous aortic origin that the literature suggested could result in a high-risk cardiovascular condition: patterns characterized by an intramural aortic course (previously "located between the aorta and pulmonary artery," or interarterial).[6,10,12,17] Unfortunately, this matter has not been totally resolved in the literature: even recently, some authors, on the basis of inexact definitions, have assumed that an intramural course is not an essential feature of malignant anomalous origin or that it varies in the general group (eg, it sometimes includes passing through an intraseptal, or even a prepulmonic or retroaortic, course).[9]

To increase the efficiency and acceptability of our study while referring essentially to ACAOS pathology, we simplified our MRI screening protocol to focus only on the location of the coronary ostia (3 per case) and the proximal course of each coronary artery.[13,19] In a later analysis of our 3165 initial cases, we found that >99% (9432 of 9495) of the expected coronary arteries (the 3 proximal trunks of the left anterior descending, circumflex, and right coronary artery) were clearly identified[19]; in 0.007% of cases (most likely involving the circumflex artery), we could not reach a definitive diagnosis (Figure 2). At this initial stage of reporting, it seems that 0.7% of this young general population has ACAOS (including R-ACAOS in 0.5% of cases) and that the total prevalence of high-risk cardiovascular conditions is 1.6%, or >5× what it was previously assumed to be (0.3%).[17]

Alternative Imaging: Echocardiography and Coronary Computerized Tomographic Angiography

In its degree of precision, MRI-based screening is a dramatic improvement over transthoracic echocardiography, which typically reported a prevalence of CAAs, or ACAOS, ranging from 0% to 0.2%.[20–22] In comparison, a recent limited echocardiographic screening study of >2000 children did not show any cases of ACAOS or high-risk CAAs.[22] The use of transesophageal echocardiography for screening is greatly limited by this method's invasiveness and cost; also, the ability to evaluate the severity of individual ACAOS cases is limited, because transesophageal echocardiography lacks precision
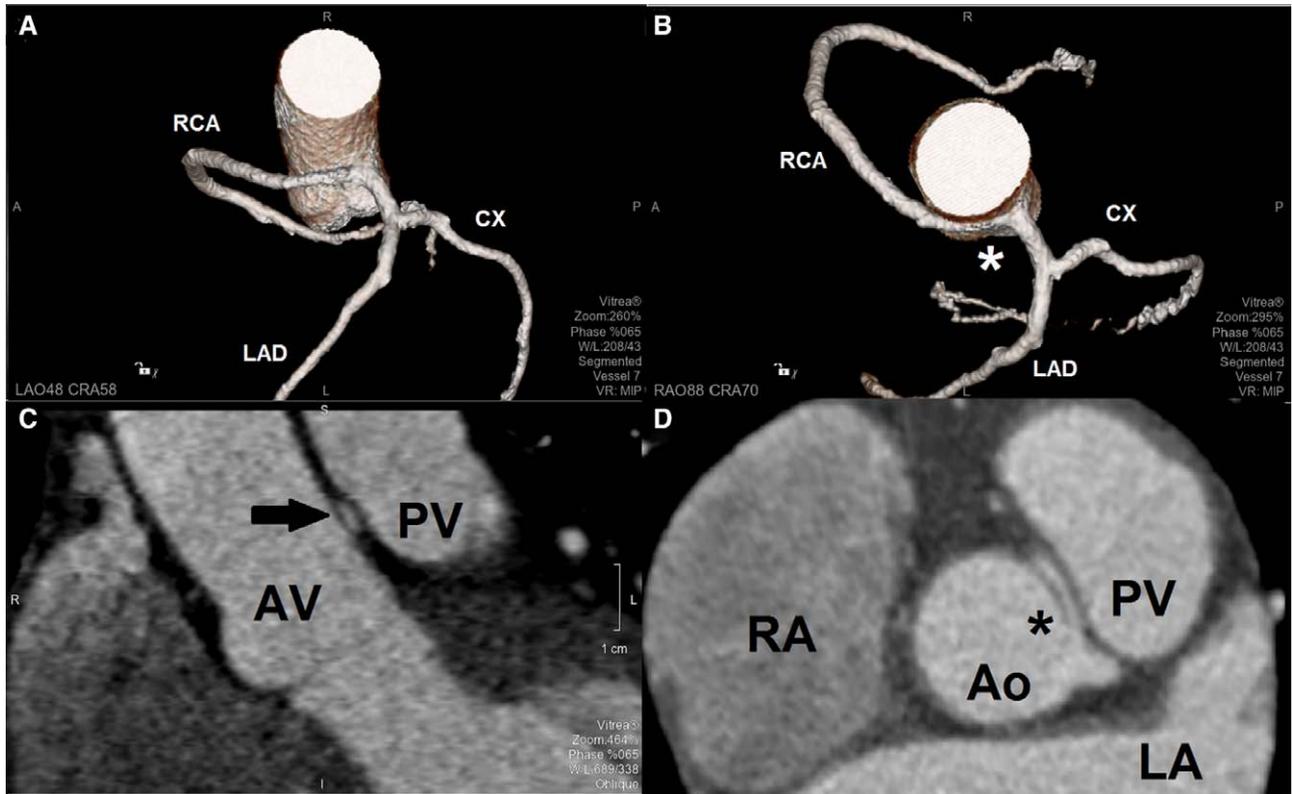
Figure 2. Computed coronary tomographic angiogram of the heart (3-dimensional [3D] reconstruction), in a case of anomalous right coronary artery (RCA) arising from the opposite sinus (R-ACAOS). **A**, in the frontal view and (**B**) in the cranial frontal view. Additionally, in tomographic source imaging, right anterior oblique cross-sectional view of the aorto/pulmonary septum (**C**), at the crossing of the ectopic artery (asterisk). Note that the lateral compression of the RCA is obvious only in view **C**; unfortunately, the wall thickness of the great vessels is not seen in this rendition. **D**, Cross-section of the aortic root at the level of the RCA proximal trunk: the artery travels from the left sinus to the right in front of the aorta (asterisk). Only intravascular ultrasonography is able to clarify that lateral compression varies during the cardiac cycle and affects the proximal segment because of the intramural course. Note also that 3D reconstruction is quite dramatic in showing the ectopic origin of the RCA (**A**), but a cranial tilt is necessary to suggest stenosis of this segment (**B**). Ao indicates aorta; AV, aortic valve; CX, circumflex artery; LA, left atrium; LAD, left anterior descending artery; PV, pulmonary valve; RA, right atrium; and RCA, right coronary artery.

in imaging cross-sectional stenosis and distal vessel size and distribution.

Coronary CTA results in more precise imaging (Figure 2) than does MRA, but the need for ionizing radiation and intravenous contrast agents makes this technique unacceptable for primary screening, especially of children. If doubt about the presence of an important CAA should arise on clinical grounds (eg, syncope or sudden cardiac arrest) or on preliminary screening tests (with echocardiography or MRA), coronary CTA may be indicated for establishing a more precise generic description of the coronary arteries. Should more precise CTA protocols become available, CTA could also be appropriate for secondary evaluation of the severity of stenosis after ACAOS has been diagnosed by screening methods (see below): in particular, CTA could potentially produce diagnostic systolic and diastolic images of the intramural coronary segment with lateral compression.

Costs of Imaging for Screening

At the end of our MRA screening project (in which MRA is proving to be ideal because of its simplicity and accuracy in a preliminary study concerning the prevalence of predisposing factors for sudden cardiac arrest in young persons), we will

have to assess the project's cost, cost/efficiency, and affordability, as well as specific populations that may benefit from routine screening ahead of certification for sports. Currently, we are operating with the support of a generous private grant, so that neither the screened students nor the schools pay for the study. The cost of cardiac MRI varies considerably, depending on the nature of the provider: it is totally different in a private practice environment than in publicly organized, dedicated groups that might operate under state sponsorship[22]; because school sports are mainly performed in this context in the United States, relevant statutes would possibly imply a public mandate. Health insurance companies have not yet issued recommendations in this regard, but effective and approved preventive screening is generally covered.

Clinical Evaluation: Symptoms and Objective Signs of Ischemia

The majority of young patients born with CAAs—including even the most serious anomalies such as ACAOS—do not have definitely abnormal, recognizable symptoms. Only serious and exceptional manifestations, that is, syncope and sudden cardiac arrest, would obviously call for immediate clinical action. This lack of patient recognition may be partially because of the
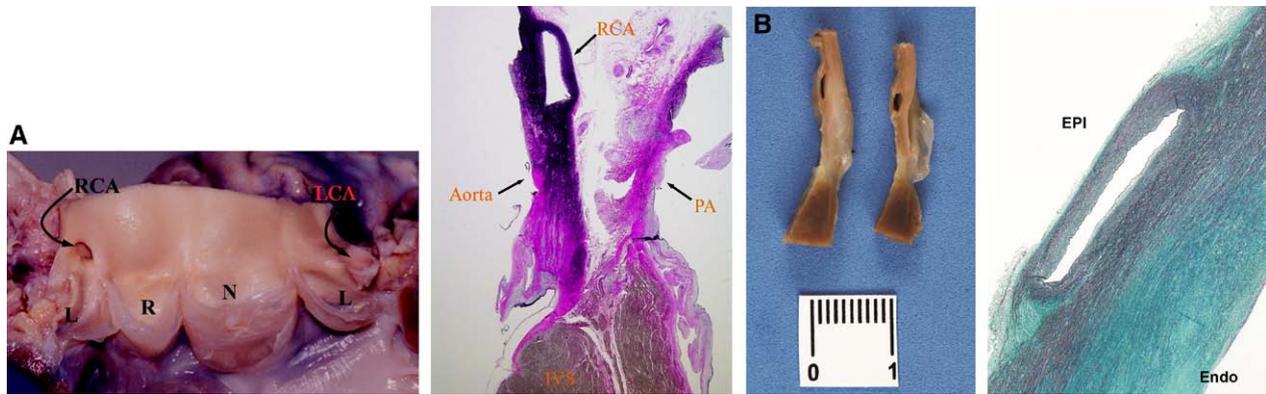
Figure 3. Histological cross-sections of the aortopulmonary roots in 2 typical cases of sudden death in young people with anomalous coronary artery arising from the opposite sinus (ACAOS), showing the detailed anatomy of the ectopic right (**A**) and left (**B**) coronary arteries, which are embedded in the aortic wall (intramural). Note that the anomalous artery is located not in the space between the aorta and pulmonary artery but within the aortic media. **A**, Anatomic (view A1) and histological findings (view A2) in an 18-year-old male basketball player who had a sudden cardiac arrest while playing in a competitive high school game. Despite aggressive treatment on the court, he was not alive on admission to the closest hospital. The autopsy revealed no significant myocardial scarring but showed the presence of R-ACAOS; the dominant right coronary artery (RCA) had an intramural course inside the aortic wall, in its 6-mm proximal segment. In the gross anatomic specimen (view A1), note the slit-like origin of R-ACAOS. Changes characteristic of athletes' hearts (hypertrophy and mild dilation) were noted. IVS indicates interventricular septum; and PA, pulmonary artery. Photo courtesy of Dwayne A. Wolf, MD, PhD; Office of the Medical Examiner of Harris County, TX. Reprinted from Angelini et al[27] with permission of the publisher. Copyright © 2002, Texas Heart Institute, Houston. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. **B**, Gross (view B1) and histological (view B2) autopsy findings (**right**) in a 14-year-old girl, a trained jogger, who had a sudden cardiac arrest while in training. She was resuscitated successfully at the scene but died 3 days later, after remaining in a coma with low cardiac output. The lateral compression of the ectopic left coronary artery (LCA) is unusually severe, both in the intramural and the more distal subadventitial sections of the abnormal artery (view B2). No signs of hypertrophic cardiomyopathy were discovered. ENDO indicates endocardial; and EPI, epicardial.

subtle presentation; for instance, mild physical limitations may be interpreted as being within normal limits and as simply proving that not everybody is born to be an elite athlete. This could also explain why SCD during strenuous activities is often the first manifestation of a CAA.[3–16] The importance of expert, sensitive history taking is indeed invaluable in this regard. Unfortunately, however, abnormal dyspnea, chest pain, and dizziness can be deceptive and nonspecific, especially in young persons.[23] In this setting, objective testing to elicit ischemic changes and especially to evaluate the severity of a given case of ACAOS has

not been studied prospectively in large series, mainly because the initial general experience with this approach has been disappointing.[24] Electrocardiographic, nuclear or cardiac MRI, and echocardiographic stress testing for myocardial ischemic manifestations in the clinical laboratory setting have frustrated clinicians by producing both low numbers of true-positive and relatively high numbers of false-positive results. In fact, some CAAs have been fortuitous findings associated with (falsely) positive stress test results (which are reported to constitute 15–30% of the reasons for diagnostic heart catheterization).[25,26] This disappointing experience with indirect evaluation of myocardial ischemia is consistent with a benign clinical history, even in athletes who eventually die of SCD.[13] In reality, in similar patients, clinicians may be missing some important modulators of the mechanism of variable stenosis (perhaps a flail-valve mechanism at the ostium that could be enhanced by higher blood flow velocity and a secondary Venturi effect, or increased aortic compliance, in exceptional cases and during physical activities, leading to more severe coronary intramural entrapment).

Pathophysiology: Imaging of the Intramural Course (IVUS, CTA, Optical Coherence Tomography)

In recent years, our center and others[25–30] have published substantial clinical evidence to suggest that all cases of ACAOS (as defined above) have some degree of stenosis at the intramural segment (Figures 2–7)[27,28] because of variable degrees of hypoplasia and lateral compression that cannot be clearly identified with coronary catheter angiography (Figure 4).[27–30] For comparison, the anatomic findings in 2 previously asymptomatic young patients who experienced SCD during sports activities
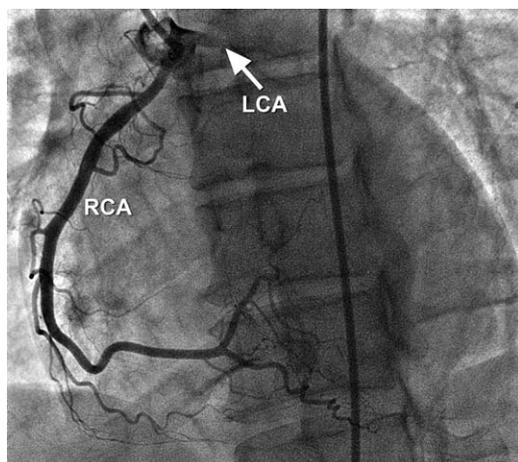

Figure 4. Coronary angiographic image in the left anterior oblique projection showing the close origin of the right (RCA) and the left (LCA) coronary arteries from the left sinus of Valsalva. No evidence of ostial stenosis is apparent in this view. The diagnosis of anomalous RCA arising from the opposite sinus and the dominance pattern are well documented by this imaging technique. Arrow indicates left coronary main trunk.
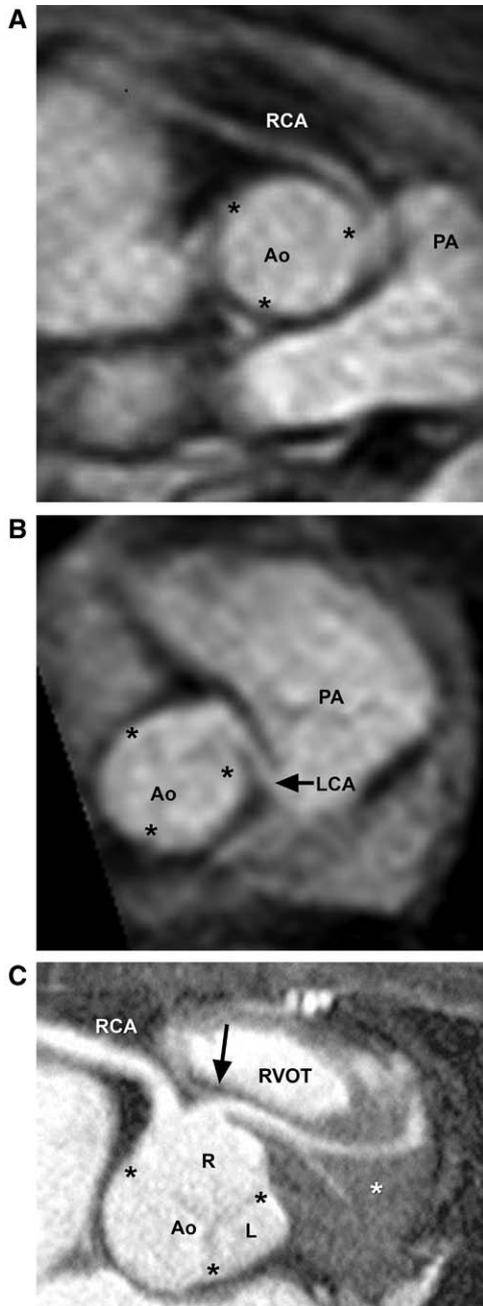
Figure 5. Screening cardiovascular magnetic resonance images of 3 typical coronary artery anomalies, which can be high-risk cardiovascular conditions, especially in athletes. The black asterisks indicate the 3 aortic valve commissures. **A,** Anomalous origin of the right coronary artery (RCA) from the left sinus of Valsalva, with a preaortic, interarterial course (right anomalous coronary artery arising from the opposite sinus). Ao indicates aorta; and PA, pulmonary artery. **B,** Anomalous origin of the left coronary artery (LCA; arrow) from the right sinus of Valsalva, with an interarterial course at the level of the aortic and pulmonary valves. **C,** Anomalous origin of the LCA from the right sinus of Valsalva, with an infundibular course, which is usually benign (also called an intraseptal course). Ao indicates aortic root; RCA, right coronary artery; and RVOT, right ventricular outflow tract. The white asterisk indicates ventricular septal myocardium. L indicates left sinus of Valsalva; and R, right sinus of Valsalva.

are shown in Figure 3. Such autopsy evidence prompted us to pursue precise in vivo imaging in carriers of ACAOS and to correlate our findings with the clinical presentations. On IVUS,

lateral compression of these abnormally coursing vessels was also shown to vary during the cardiac cycle, being worse in systole and further increasing during exercise (Figure 6; see also Figures 2, 5, and 8, which show newer, alternative imaging techniques).[28] Although both MRA and CTA can reliably diagnose ACAOS (Figure 2), neither of these methods can yet accurately evaluate the severity of stenosis in a given case. Recently reported initial data from our large series of IVUS-based clinical studies in adult patients with R-ACAOS (63 cases) have shown strong evidence that the severity of stenosis correlates with the occurrence of ischemic symptoms (ie, angina, dyspnea, or syncope, in addition to SCD), both at baseline and after stenosis is resolved by stent angioplasty, which we tried experimentally in some of the more symptomatic cases.[26]

On the contrary, in all other types of ectopic aortic origin of coronary arteries, IVUS investigations have preliminarily revealed that stenosis and, hence, myocardial ischemia do not occur (in the prepulmonic, intraseptal, retroaortic, or retrocardiac courses, as illustrated in Figure 1). In cases of ACAOS, further critical studies (in methods and prospective design) are needed to define discriminating parameters of clinically significant stenosis (such as mild or serious versus at rest or during exercise), but it seems that IVUS could provide a sensible new means of evaluating these parameters. During exercise, tachycardia (which increases coronary flow during systole) and an increased stroke volume (which augments ascending aortic expansion) may especially increase the severity of the ischemic burden. By studying these variables, we should be able to evaluate the effectiveness of clarified diagnosis and novel treatment protocols at reducing the mortality rate (especially in children and young athletes) and clinical symptoms (in adults).[25,26,29] In 63 cases of R-ACAOS examined with IVUS, the severity of resting stenosis varied widely, involving between 4% and 83% of the cross-sectional area; only 56% of all patients studied with IVUS were tentatively treated with stent angioplasty based on the severity of symptoms and stenosis.[26] Furthermore, after >1 year, an analysis of patients with R-ACAOS who received stents (because of more significant symptoms, stenosis, or both) suggested that their postoperative functional status was greatly improved, confirming our general pathophysiological theory.[26]

At this time, the challenge is to carry the analysis of functional stenosis to an even more subtle level, likely by building curves of the cross-sectional area of instantaneous stenosis during the whole cardiac cycle (Figure 7 and Movie in the Data Supplement). For this level of sophistication and precision, IVUS may have limitations in spatial and temporal discrimination that only the next generation of imaging methods, including possibly optical coherence tomography, can overcome (Figure 8). Indeed, optical coherence tomography has a resolution 10× better than that of IVUS.[31,32] Current limitations of the use of optical coherence tomography in cases of ostial stenosis come mainly from the absence of an electrocardiographic signal display and the need to completely eliminate blood from the area being scanned by the infrared laser; achieving this aim may be difficult when the guiding catheter is positioned at the very site of tangentially oriented, severely obstructed ostia, as necessarily implied in ACAOS.[25]
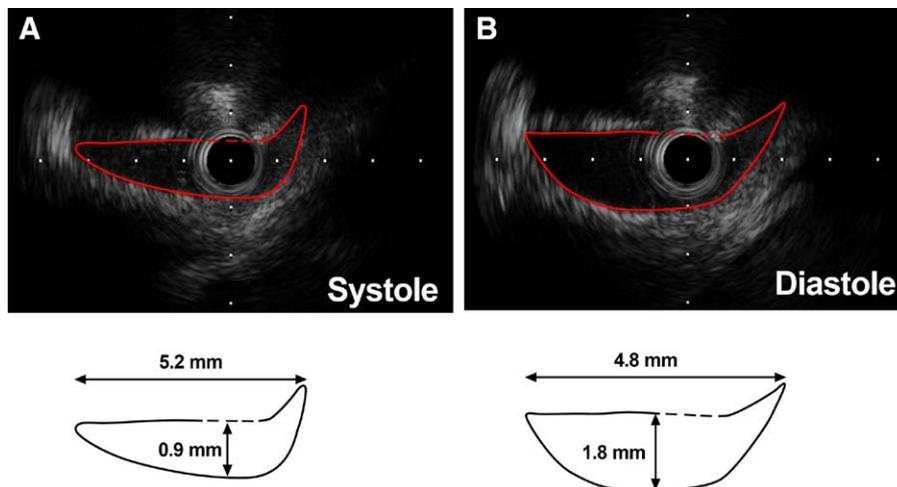
Figure 6. Systolic (**A**) and diastolic (**B**) intravascular ultrasound (IVUS) images from a patient with symptomatic right anomalous coronary artery arising from the opposite sinus. During enhancement with a continuous intracoronary infusion of a saline and blood solution, the inner edges of the cross-sectional lumen were easily discerned. The diameters were 0.9 mm in systole and 1.8 mm in diastole, as shown in the cartoon below each image. The artifact in the middle of the images corresponds to the cross-section of the recording probe. **C**, IVUS cross-sectional image of a segment distal to the intramural one (**A** and **B**). Intimal thickening from atherosclerotic build-up is clearly seen in this extramural segment (and is consistently missing in the intramural segment). This segment of the artery is round and has a 3.5-mm uniform diameter, with an area of 19.34 mm². The resulting area of stenosis is 71%.

Conclusions

Any effective strategy for preventing SCD in young persons will need to be formulated in the light of novel imaging techniques that can be applied effectively in large, at-risk populations. According to current standard recommendations, obtaining a history and physical examination is all we can do to prevent SCD. The disappointing results of this policy are obvious: we need more effective yet acceptable methods, which may soon become available and practical. Claiming that SCD in young persons is a rare occurrence clearly seems an inadequate response to the tragic, recurring problem of deaths on the playing field. The significant advantages of novel screening methods compared with traditional ones are obvious, especially for detecting CAAs. In

particular, the recent introduction of screening MRA protocols for this purpose has dramatically improved reliability and efficiency without introducing significant side effects. Enhanced accuracy of screening tests also decreases the need for costly secondary evaluations prompted by false-positive or false-negative initial screening results obtained with other methods.[13] At this preliminary stage, we can at least start claiming to know precisely how many people in our communities live with potentially significant CAAs and are at an increased risk of unexpected, but potentially preventable, catastrophes or disabilities. The US population includes ≈92 000 000 young persons (aged 12–35 years), of which 644 000 (0.7%)[19] are expected to have some type of ACAOS. We do not yet know how many of them will die
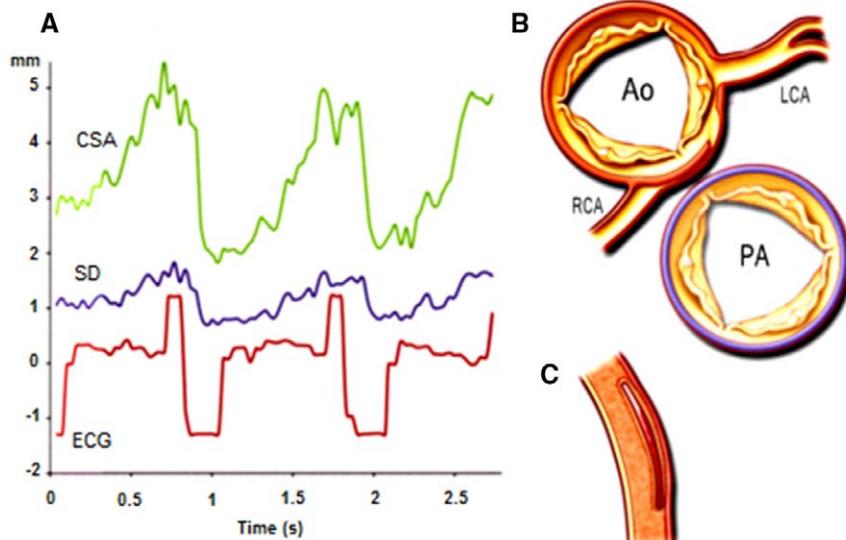

Figure 7. Instantaneous stenosis during the whole cardiac cycle in anomalous origin of the right coronary artery (RCA) from the opposite sinus of Valsalva. Systolic expansion of the aortic root leads to significant worsening of lateral compression, as indicated by the chart (**A**; **left**), which shows the variation in the cross-sectional area (CSA; blue line) during the cardiac cycle; the CSA increases from 2.3 to 5.1 mm² in diastole, whereas the short diameter (SD) of the intramural RCA (green line) increases from 0.8 to 1.5 mm. This is an example of severe functional stenosis. The chart readings were obtained by calculating each parameter of intramural stenosis in instantaneous intravascular ultrasonography (30 frames per second). The red line represents the ECG. **B**, **Top right**: Schematic cartoon illustrating the mechanism of stenosis. **C**, **Bottom right**: Cartoon showing a cross-sectional systolic frame of the intramural course. The 3 panels move synchronously (for the timing, see Movie in the Data Supplement).
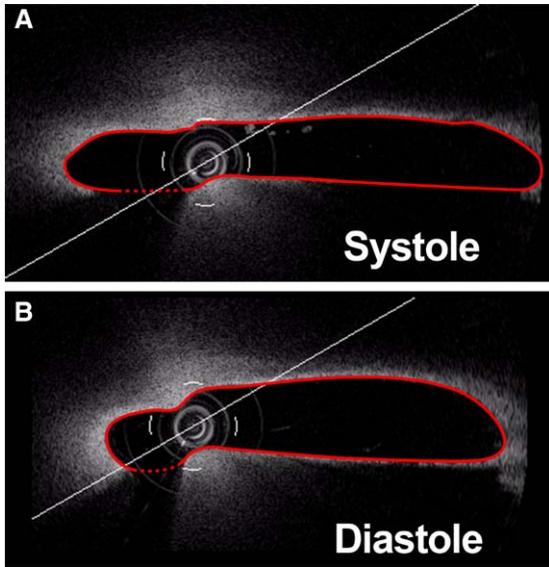
Figure 8. Optical coherence tomographic (OCT) images in systole (**A**) and diastole (**B**), showing the much improved definition of the intravascular anatomy afforded by OCT. Potentially, instantaneous changes in the severity of stenosis during simulated exercise could be much more easily quantified by OCT than by intravascular ultrasound. The probe marks (circle) show the calibration in the images (diameter=0.9 mm). In both **A** and **B**, the interrupted line indicates the beginning of the slit-like orifice of the right coronary artery (the C sign typical of tangential origin).

cardiovascular conditions in SCD versus non-SCD fatalities in a defined population throughout its full lifespan.[13]

In an attempt to foresee the future, Figure 9 shows a novel algorithm that could become feasible, cost-effective, and useful for preventing SCD in young persons despite the current absence of definitive evidence to support this approach. The proposed algorithm emphasizes the role of cardiac MRI, because the use of this modality would likely make screening simpler and more effective in high-risk subpopulations. Such a change in management (from the current reliance on history and physical findings only) should be validated by further prospective studies designed to evaluate its practicality, cost, and effectiveness in preventing SCD in different populations (eg, sedentary persons versus sportsmen).

Recent progress in the clinical understanding of CAAs indicates that, for epidemiological purposes, ACAOS is the only significant subclass of CAAs that can cause SCD in young athletes and military recruits. It is also the only subclass that can cause clinical symptoms of ischemia. With MRA, screening is quick and effective, with a low incidence of false-positive and false-negative findings and an accuracy of >99%, but the cost of this method may preclude its widespread use. If initial MRA screening detects ACAOS (and this diagnosis is confirmed by further studies), further subclassification will be required to identify which patients could be at high risk, especially during exercise, versus which patients would have a more benign prognosis.[13] Currently, the severity of stenosis at the intramural proximal coronary course seems to be the most important variable to be evaluated, and only sophisticated invasive imaging techniques, such as IVUS or optical coherence tomography, can adequately evaluate this variable. Persistent challenges include identifying those patients for whom invasive imaging is justified, the indications for intervention, and the optimal type of intervention.
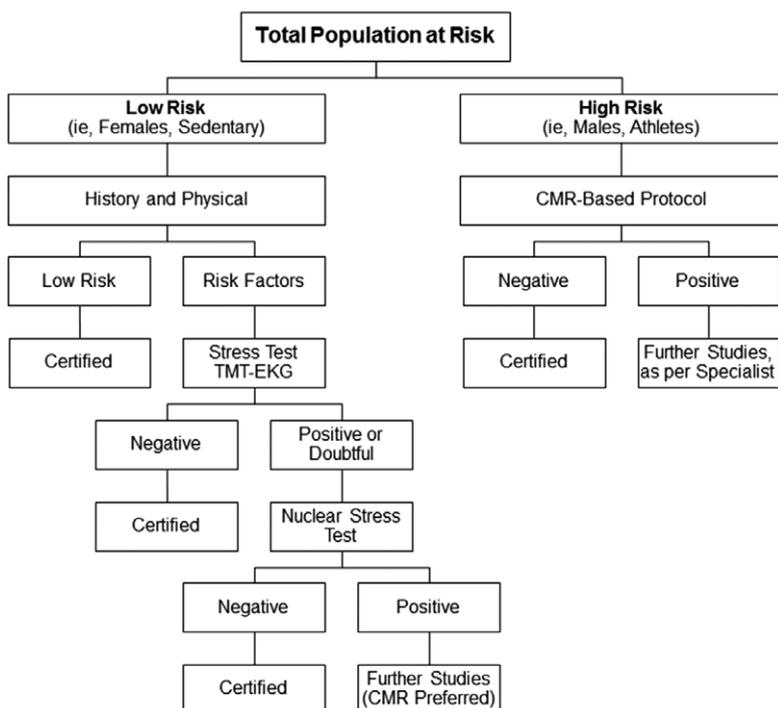
of this condition. In a parallel study at our center,[13] we are pursuing fundamental answers to the questions related to mortality, in collaboration with the Harris County Forensic Center: this project covers the great majority of cases of out-of-hospital SCD in the city of Houston, which has a population of 4 500 000. In this study, we are attempting to more accurately determine the prevalence of high-risk

Figure 9. Proposed novel algorithm for certifying young persons (aged 11–15 y) at the start of participation in sports activities. Persons with (1) severe symptoms (especially syncope), or (2) a positive stress-test result, or (3) choice of a career in an exceptionally strenuous sport (ie, college or professional football, soccer, basketball), or (4) a need for life/health insurance should undergo subclassification by means of accurate imaging, namely intravascular ultrasonography (IVUS). Criteria for critical, disqualifying severity of stenosis involving anomalous coronary artery arising from the opposite sinus (intramural stenosis by IVUS) are to be established. CMR, cardiac MR; and TMT, treadmill test.

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