Trends in Cardiovascular Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Critical update and discussion of the prevalence, nature, mechanisms of action, and treatment options in potentially serious coronary anomalies

Paolo Angelini*, Carlo Uribe

The Center for Coronary Artery Anomalies, Texas Heart Institute, Houston, Texas, United States

ARTICLE INFO

Keywords:
Coronary artery congenital anomalies
MRI screening of ACAOS
Sudden cardiac death
Intravascular ultrasound imaging
Coronary anatomy
Intramural versus intraseptal course

ABSTRACT

As widely discussed in recent literature, coronary artery anomalies only occasionally lead to potentially serious myocardial ischemic events. The most important group of coronary anomalies has been called anomalous coronary artery origin from an abnormal sinus or a site in the ascending aorta (ACAOS). Only some cases of right- or left-sided intramural-course ACAOS (R-ACAOS-IM or L-ACAOS-IM) can potentially cause significant symptoms or sudden cardiac death, typically during exertion in athletes. After an ACAOS-IM case is qualitatively identified, it is necessary to establish the severity of associated stenosis (which is always present to some degree in ACAOS-IM). The 3 stages of a comprehensive diagnostic process are: 1. initial screening of high-risk populations (young elite athletes, optimally by use of magnetic resonance imaging [MRI]) to identify the prevalence of similar cases in large populations (the denominator of any risk calculation); 2. evaluating symptoms (chest pain, syncope, or sudden death) and performing stress testing; 3. in patients found to carry ACAOS-IM, evaluating the severity of coronary obstruction by intravascular ultrasonography, which is an objective, definitive, and quantifying imaging modality for this condition, essential in selected carriers of such anomalies. The possible treatment alternatives are discussed and updated.

Introduction

A recently completed magnetic resonance imaging (MRI)-based screening study of the prevalence of potentially high-risk coronary artery anomalies (CAAs) in a large general population of adolescents indicates that more than one million Americans have anomalous origin of coronary arteries from opposite sinuses of Valsalva with intramural course (ACAOS-IM, prevalence of 0.44%), which has the potential to cause significant coronary stenosis and related symptoms or lethal events such as sudden cardiac death (SCD) [1]. Because SCD is most frequently unheralded, generalized screening studies are logical to pursue in young athletes or military recruits but are not yet proven to be justifiable for preventing SCD. Only specific prospective studies will be able to confirm this point.

The singular association of ectopic coronary arteries' intramural course with stenosis is the reason why these are the only types of CAAs of potential clinical importance. Great individual variability in severity of stenosis is possible, and not all cases of IM anomalies indicate intervention. This variability, in addition to the involved individuals' symptoms and the specific risk of unheralded SCD (mainly in athletes), implies the need for an in-depth understanding and evaluation of these anomalies' individual presentations to enable justifiable treatments. ACAOS is currently understood as complex and variable, and the potential clinical risk is initially identified by anomalous origin and proximal course (IM course is the only one that has a consistent possibility of causing coronary dysfunction from coronary stenosis [2,3]). Both the location of the coronary ostium and proximal course can be confidently identified by screening MRI but not usually by history and physical exam or stress testing [1]. Ectopic origin alone is not an anatomic marker of high risk, nor is it by itself the cause of coronary insufficiency. Severe functional stenosis is intrinsically related to intramural course (IM, inside the aortic wall) that results in lateral dynamic compression secondary to aortic phasic pulsatility and exertion.

The size of dependent myocardial territory affects greatly the clinical consequences of ACAOS-IM: Right coronary artery (RCA) anomalies (R-ACAOS-IM) are more frequent (about 3:1 ratio) but usually have less functional importance (in terms of physical limitation and risk of SCD) than left coronary artery (LCA) anomalies (L-ACAOS-IM) [2,3]. The functional mechanism of ACAOS-IM involves both fixed (baseline) and dynamic compression of

* Corresponding author.
E-mail address: pangelini@texasheart.org (P. Angelini).

https://doi.org/10.1016/j.tcm.2022.05.007
1050-1738/

the entrapped IM coronary segment that causes variable lateral-compression stenosis, which is worse in systole. Aortic expansive pulsation leads to phasically increased wall stretching that worsens compression of the IM coronary lumen by increased radial stress, especially during exertion. Specifically, exercise 1. causes tachycardia, which leads to increased systolic time (percentage of systolic time narrowing per minute) and decreased diastolic time (which also reduces global blood flow); 2. results in increased cardiac output and stroke volume (cardiac work); and 3. maximizes demand/supply imbalance, potentially causing ischemia during strenuous exertion (especially in young unaware athletes who are testing their own physical capacity for the first time while competing, leading to highest mortality at the age of 18-19 years [4]). Documentation and quantification of ischemia are the most challenging issues in ACAOS-IM evaluation [2,3,5-11].

Nomenclature of ACAOS

To improve communication among involved professionals about all different coronary anomalous patterns and their associated functional repercussions, the terminology of CAAs must be clarified and, hopefully, shared. Along these lines, our group has elaborated on and endorsed for many years a simple and synthetic system [1] that involves (1) identifying with an initial abbreviation the anomalous, involved artery (R- or L-) [or, independently, the left anterior descending (LAD-) or circumflex (Cx-) artery]; (2) identifying the basic defect (ACAOS); and especially (3) identifying and labelling the type of proximal course of the ectopic artery, while crossing the heart from the ectopic origin toward the defining myocardial destination, on the opposite side of the heart. To be useful, terminology should be able to synthetically indicate course-related risk factors: Only the IM course can be intrinsically risky, whereas non-IM courses—namely the prepulmonic (PP), intraseptal (IS), retroaortic (RA), and retrocardiac (RC) courses—have a benign prognosis (Figs. 1-8, Videos S1-S3). Notably, IM course is also observed in cases with origin from the ascending aorta above the sinuses of Valsalva, such as seen in high and commissural origin [2,3]. Alternative nomenclatures, mainly used by pediatric centers, use terms like anomalous aortic origin of coronary arteries (AAOCA: distinguished only as left [AAOLCA] or right [AAORCA]) [9,12-18] or anomalous left or right coronary arteries (ALCA and ARCA), which we believe are too broad and vague to be clinically useful, while erroneously defining multiple subtypes as single entities.

Diagnostic process

As we anticipated, screening-MRI studies are useful for identifying the size of the potentially associated issue (SCD in athletes with ACAOS), preventively certifying athletes, and clinically explaining SCD in athletes [19]. Unfortunately, these studies have not been able to clarify the extent of prevention by screening and its cost-efficiency in different milieus (e.g., the US military vs the general population in a Central American country).

The essential maturation of our knowledge of CAAs was critically enhanced by in vivo, dynamic, and high-precision imaging that was uniquely achieved by the introduction of intravascular ultrasonography (IVUS) [5-8,20]. Early reports of pathologic anatomy findings sporadically mention “intussusception” of the ectopic coronary artery inside the aortic root media, but this abnormality’s individual severity was never precisely correlated with clinical consequences in autoptic studies [21–23] before the popularization of IVUS.

Eventually, our center and others came to understand that only by functional imaging during the cardiac cycle can an observer quantitatively identify the essential features of milder (end-diastole) or worse narrowing severity (end-systole) and worsening with exertion [2,3]. As mentioned above, in recent years, several authors [5-8,24] have reported mostly short series of ACAOS-IM cases studied by IVUS. Now, most experts agree that it is essential to quantitatively determine an individual patient’s prognostic risk by means of IVUS-quantifiable cross-sectional area (CSA) at the site of worst stenosis versus at the distal (extramural) reference artery (Figs. 6-8, Videos S1-S3). This process of evaluation is essential to understanding the general pathophysiological mechanism and to selecting interventional candidates jointly with symptoms, history of syncope or sudden cardiac arrest (SCA) or SCD, and stress testing. Very rarely, differently than in acquired coronary artery disease (CAD), acute myocardial infarction or SCD occurs at rest. (Such exceptional events probably occur in critical-stenosis cases of L-ACAOS-IM.) Generalized medical treatment (only periodic follow-up with the facultative prophylactic use of beta blockers) has not been proven effective by small, preliminary studies in either athletes or sedentary CAA carriers [2,3].

Unfortunately, current clinical decisions are still frequently based on inadequate diagnostic methods that may describe qualitatively but not quantitatively markers of risk, as shown even by advanced transthoracic echocardiography or computerized tomography angiography (CTA) [16,18,25]. Unfortunately, many patients are still being advised to have surgery on the basis of nonspecific

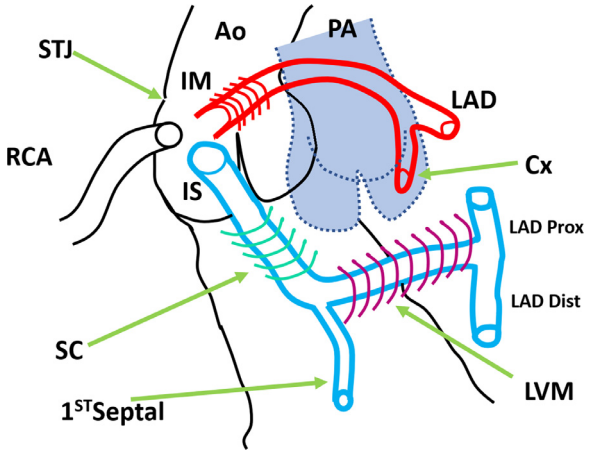


Fig. 1. Schematic showing artificial superimposition of the two essential forms of L-ACAOS, which are frequently confused with each other: L-ACAOS-IM (intramural, aortic, in red) and L-ACAOS-IS (intraseptal or infundibular, in blue). These are shown together to illustrate the essential differences between them. 1. Both anomalies originate from the same site at the right sinus of Valsalva, separately or from a common single ostium and coronary main trunk. 2. The IM variety features intramural proximal segment of the initial section (inside the aortic media, at the level of and parallel to the sinotubular junction, adjacent to the aortic root) with dynamic, variable stenosis. Distal to the IM segment, the left coronary is epicardial and retropulmonary in location but is essentially normal. 3. The intraseptal (IS) variety has an initial short epicardial course, eventually tilted caudally, that is extramural for its entire length and that *does not cross* the closest aorto-pulmonary junction or the aorto-pulmonary septum (suggesting the reason why this variety is also improperly called “interarterial course” [IAC]: that this segment is not stenotic in cross-section), and it quickly turns down toward the supraventricular crista (SC, where the intramyocardial tissue has right ventricular pressure, without a myocardial bridge effect) at the outflow tract of the right ventricle (green lines indicate its right ventricular intramyocardial course), while the next 2-3 cm run inside the left ventricular myocardium (LVM, with a mild myocardial bridge effect, at purple crosslines) and return epicardially at the mid-level of the epicardial left anterior descending artery, which it joins. (Hence, the proximal bifurcation goes cephalad to the circumflex, while the distal goes to the apex.) No fixed stenosis at baseline has ever been identified by IVUS in the IS variety, at any level. Note that the 2 anomalies take opposite initial courses around the pulmonary artery root. Abbreviations: LAD indicates left anterior descending; Cx, circumflex; 1st septal, first septal branch off the left main or LAD; STJ, sinotubular junction; Ao, aorta; PA, pulmonary artery; IM, intramural proximal course; IS, intraseptal course; SC, supraventricular crista. See also: Link to 3D-animation in Video S1 in the online supplemental information.

symptoms but without proper quantification of their CAA's severity, and even without a correct diagnosis (see section below on L-ACAOS-IS course). Also, in this regard, it is fair to underscore that CTA images are typically read only during end-diastole (the portion of the cardiac cycle when arterial anatomy is most stable in the beating heart but has less severe stenosis), while also aortic distensibility (degree of enlargement in systole) may differ significantly among patients.

Another confusing practice originates from the fact that many clinicians and investigators continue to describe CAA patients' symptoms and mortality risk as due to "unknown" mechanisms while alluding to multiple non-quantitative, associated deformities as alternative factors—slit-like ostium, acute angulation, tangential course, valve-like ostium, interarterial course (IAC), IAC without IM course, hypoplasia. All these features can indeed be markers of stenosis, but only IVUS imaging can yield the quantitative global stenotic site CSA (Figs. 4-8, Videos S1-S3).

In particular, we believe that the term IAC [6,8,9,12,14,26,27] should be generally avoided because it alludes to an incorrect notion tentatively suggested by some pathologists and clinicians who initially thought the mechanism of coronary insufficiency in CAA was caused by compression (a scissor effect) of the ectopic artery located in the space between the aorta and the pulmonary artery [21-24,28]. Both the IAC concept and term should be avoided because this condition is not the cause of ischemia, but especially because only in cases with an IM course is the mechanism of external dynamic compression correctly understood and the stenosis quantifiable: the essential cause of coronary insufficiency (Figs. 3, 7, and 8, Videos S1-S3). This misconception especially refers to "IAC without IM course," which has even misled many clinicians to identify as surgically "operable" (needing an operation) those cases perceived as having an interarterial course, when they had essentially IS course (benign), passing from an initially subepicardial and extramural location, into the *crista supraventricularis* (at the right ventricular outflow tract) and finally at the upper ventricular septum, to join the epicardial left anterior descending coronary artery (Fig. 1 and Video S1). The IS course is by itself a consistently benign variant anomaly not requiring any surgery (see further discussion below). The distal portion of this variant, inside the interventricular septum, is always intramyocardial and shows mild systolic narrowing, as a myocardial bridge (generally benign). The relevance of persistent confusion in this regard is revealed in the frequent mention, in reports of surgical interventions in series and registries of CAA surgery, that 5-19% of the patients sent to surgery for "unroofing" as IAC cases were shown at surgical exploration to have neither an IM segment nor stenosis to justify intervention [14,24,26]. The same surgical techniques designed for alleviating the scissor effect or IM course at the interarterial site were developed to cause pulmonary dislocation or to make intracardiac repairs (neither of which can affect IM course) [11,14,17,24,27,29].

Recently, the opinion was circulated in pediatric cardiovascular circles [24,27] that fixed stenosis is frequently present in cases of L-ACAOS-IS that may cause myocardial infarction and require surgical treatment. This opinion remains highly questionable (Figs. 1 and S1), and we should state clearly that only IM-related stenosis may require repair; spontaneous coronary spastic events can be observed in L-ACAOS-IS but should be treated (if confirmed with acetylcholine testing) with vasodilators (see section titled Coronary Spasm and CCA). Most likely, the few cases recently presented [24,27] to support the theory that L-ACAOS-IS has fixed stenotic segments (although it is unclear at what level, or by what mechanism) that need interventional treatment should be strongly questioned. These were probably cases of spontaneous coronary spasm, which is reproducible by ACh testing or stiff coronary guidewire advancement, by artifact onset. The absence of any cases of L-ACAOS-IS (vs 21 cases of L-ACAOS-IM) in Eckart and colleagues' study of SCD and its causes among 23 million military recruits is strong evidence of this anomaly's benignity [4]. Incidentally, L-ACAOS-IS is probably slightly more frequent in the general population than L-ACAOS-IM (definitive data are not yet available).

In ACAOS-IM, the sometimes mentioned "hypoplasia of the IM segment" in the involved ectopic artery indeed occurs as a separate, fixed, and mildly stenotic factor with respect to lateral compression-related dynamic stenosis (Fig. 7). Coronary hypoplasia should be measured in a cross-section orthogonal to the coronary longitudinal direction, as circumferential shortening quantified as the difference between the circumference (in mm) of the distal extramural segments minus the proximal IM circumference, divided by the distal circumference (Fig. 8A). Intramural coronary hypoplasia is common and mild (contributing 0-38% to the stenosis), but it is included in IVUS measurements [2,3] and is automatically treated by surgical unroofing, bypass grafting, or coronary stenting.

There are 2 main reasons why IVUS is not more frequently used on clinical grounds. First, most physicians who initially provide primary care for this pathology treat pediatric populations and are not familiar with IVUS. For this reason, we believe that all specialized centers for treating CAAs must include expert interventional cardiologists. Second, selective cannulation of R-ACAOS-IM or L-ACAOS-IM by standard guiding catheters is technically difficult to accomplish because the artery's ectopic location is associated with a slit-like, tangential ostium (and in severe cases, the cross-sectional diameter is less than 1 mm—the crossing profile of an IVUS probe, whereas the guiding catheter is usually 2 mm in diameter; see Fig. 7 and Videos S1 and S2). Special, dedicated guiding catheters have been developed that have a modified tip, tilt at 90° from the normal Amplatz curve (Fig. 5, Video S3) [30]. Selective ostial access is also essential for enabling optical coherence tomography (Fig. 8), which requires selective contrast injections to displace blood and permit imaging [2].

In terms of operational recommendations, the traditional official position is that IVUS (currently, the state of the art for describing such asymmetric coronary stenosis) is too laborious and unproven to recommend. Although they may be correct in stating that experience with IVUS (and stenting of CAAs) is still incomplete, those authorities avoid discussing the need for stenosis quantification to justify any kind of repair and appropriate interventional planning [12,31-33]. Currently, closing this persistent knowledge gap is a priority (Table 1). Our current operative proposals [2] for potentially serious ACAOS-IM focus on stenosis found in adolescent or adult patients who are physically active, symptomatic, or have a positive-stress test: In them, IVUS imaging could be essential. In cases of R-ACAOS-IM, IVUS-proven CSA stenosis of more than 55-60% at rest, in diastole, and 50-55% in L-ACAOS-IM (Figs. 4 and 6) are credible markers of potentially severe disease, capable of causing SCD or limiting symptoms in athletes (because stenosis becomes functionally 10-30% worse during exertion). We still recognize that this policy will have to be supported by larger, prospective, longitudinal studies demonstrating that successful interventions (with stents or with surgical revascularization) can indeed reduce or prevent symptoms, improve stress testing findings, and reduce mortality risk better than every other alternative [2,3]. Our initial experience (see Fig. 3 for details on R-ACAOS-IM, and separately for L-ACAOS-IM) is extensive (the largest reported by a single center) but unfortunately still essentially single-institution-based. In particular, it must be understood that stenosis is the basic cause of ischemia, and stent angioplasty is currently the preferred treatment option for R-ACAOS-IM at our referral center (because there is no coronary atherosclerotic disease; instead, R-ACAOS-IM features smooth and easily passable stenosis, as shown by IVUS, that can be treated by a catheter procedure, with reliable early and late results and same-day hospital discharge). Stent an-

Table 1
Approximate value scores of recommendations for diagnosis and treatment in R-ACAOS-IM.

	Medical (observational)	Surgery	IVUS/PCI
Time in use (y)	40	15-25	20
Efficacy, present results	Poor-quality	Moderate	Small
Accuracy of diagnosis	+/++++	++/++++	++++/++++
Reliability of treatment	+/++++	+++/++++	++++/++++
Acceptability	++/++++	++/++++	++++/++++
Late results	+/++++	+++/++++	+++/++++

In this table, we tried to rate empirically the current state of our knowledge while recognizing the residual gaps that need to be eliminated by more extensive, prospective, controlled, and multi-site studies. De facto, medical treatment (essentially by clinical observation of symptoms) is the most frequently used mode of treatment in R-ACAOS-IM in cases that subjectively appear mild to clinical observers, followed by the surgical and finally by IVUS-based PCI (currently dedicated to rarer cases because of limited local experience). "Time in use" refers to how long the treatment has been in clinical use. "Efficacy, present results" refers to the results of treatment by empirical protocols that are commonly considered standard-of-care despite the lack of justifiable recommendations, controlled studies, and adequate follow-up data. "Accuracy of diagnosis" refers to the accuracy of standard-of-care diagnostic preoperative work-up. "Reliability of treatment" refers to how often we believe the available treatments potentially function, and how much their effectiveness varies among practitioners. "Acceptability" refers to how widely these treatments are accepted by patients and their families (although no objective comparisons are available). "Late results (evidence)" refers to the late-term comparative results of treatment (which are not yet available, even for late mortality risk). The scoring crosses evaluate empirically the different variables in comparable candidates. A similar evaluation in appropriately controlled cohorts needs to be available to justify final acceptable recommendations. Further studies are urgently needed. Statements by official organizations (eg, "classes") are generically not yet justifiable. Abbreviations: IVUS, intravascular ultrasonography; PCI, percutaneous coronary intervention.

gioplasty procedures also include immediate demonstration of success by IVUS at the end of the procedure, whereas surgery apparently entails a 10% rate of early reoperation for residual/progressive stenosis because that evidence is not available during the intervention [14,15,17]. Our group had no in-hospital or 5-year mortality in a continuous series of 42 R-ACAOS-IM cases in which stenting was used to treat IVUS-confirmed serious stenosis. Functional class was greatly and consistently improved in this serious R-ACAOS-IM group, whereas a control cohort with milder symptoms treated medically was found to have less than 55% CSA stenosis at rest, and stable symptomatic status at baseline and at 5-year follow-up (Fig. 3) [3].

Hemodynamic stenotic testing by fractional flow reserve (FFR or iFR) [6] is also obtainable by noninvasive computerized computed tomographic angiography/instant wave-free ratio (CTA/iFR). Using CTA or iFR involves the interpretation of CTA images by sophisticated artificial-intelligence algorithms that determine flow by extrapolation. (Flow is not measured directly and precisely; rather, it is estimated from the imaging data obtained about stenosis). This method was originally approved to quantify the hemodynamic severity of stenosis (by pressure wire) and correlate it with short-term prognosis (1-year) of mild or moderate atherosclerotic coronary artery disease evaluated by catheter angiography (in CAD). A CTA/iFR less than 0.80 or 0.89 (obtained noninvasively and at rest) is claimed to correlate with a stenosis severity greater than 70% in patients with CAD and could possibly have a future role in the diagnosis of ACAOS-IM severity (not approved as yet). Approval of its use in congenital, dynamic stenoses as in ACAOS-IM [31,33] is still questionable. This approach's implied limitation is that prognosis in ACAOS-IM is essentially related to exertion, while measuring fractional pressure or FFR involves administering a vasodilator (adenosine) to increase coronary blood flow but not cardiac work or stroke volume. Additionally, the 0.80 FFR value was selected for CAD patients, in whom it would predict 1-year progression of disease (causing major clinical events), which does not necessarily apply to ACAOS-IM patients. Also, the presence of a straight and rigid guidewire in a curved artery (especially an intramyocardial one) can frequently lead to spastic stenosis artifact (which should be ruled out by selective angiography or IVUS).

Another potentially diagnostic noninvasive technique to evaluate ACAOS-IM is virtual angioscopy [24,26]. This technique is based on magnetic resonance angiography or CTA tridimensional volumetric reconstruction of the inner aortic lumen of a suspected ostial stenosis. Some authors have promoted using these images to measure the ostial size of ectopic arteries (and thus slit-like morphology and severity of stenosis). However, such imaging is liable to artifact caused by the angle of exploration, diastolic-only imaging, and lack of distal vessel CSA measurements to measure stenosis [26].

Medical treatment has not been prospectively studied by modern methods (including correlation of their use with symptoms and severity of stenosis). The experience of Malhotra et al [34] in a multi-year project at a soccer camp is illuminating in this regard: A typical player with unrecognized ACAOS-IM (despite echocardiography-based screening) continued participation until he had SCD on the field. (This is called an observational follow-up in an individual not diagnosed correctly and never considered for interventional treatment or disqualification.)

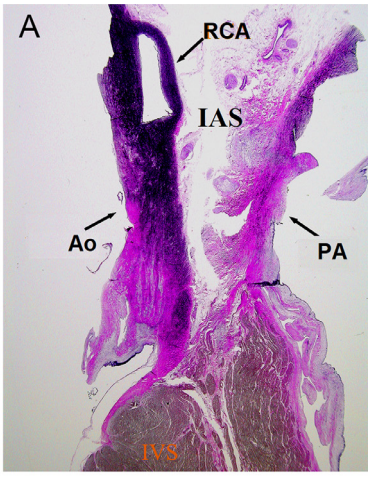
In this initial general discussion of ACAOS-IM, we focused on updated general concepts. The following technical discussion ("Treatment options") focuses on technical issues in the treatment of ACAOS-IM.

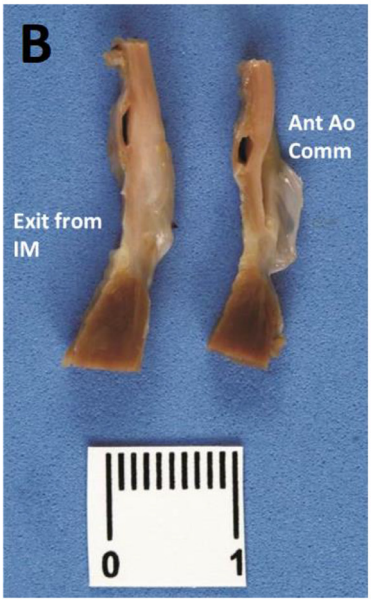
Treatment options

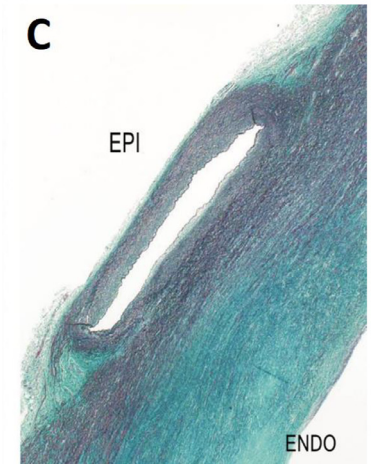
R-ACAOS-IM cases

Current practice in the interventional treatment of ACAOS [2,3,6-8,20,30,32] can be summarized in these terms:

1 Significant R-ACAOS-IM treatment (Figs. 6 and 7, Videos S2-S4) generally depends on data from a selectively ordered IVUS evaluation prompted by symptoms, lifestyle (sports, military training), stress-testing and cardiac MRI (if available for special populations, like athletes) results, and consent. The factors that finally support intervention, especially in young athletes [3], are (a) chest pain, especially if it is disabling and induced by exertion (and which can be typical or atypical, depending on its reproducibility with exertion [3]); (b) dyspnea on exertion; (c) dizziness or syncopal spells with exertion; (d) lifestyle involving athletic-level activities (as part of precertification); (e) history of SCA or aborted SCD; and (f) positive nuclear myocar-







dial stress testing, preferentially by treadmill (to document ischemia in the dependent myocardium and to establish a control for the eventual postoperative follow-up, if needed). Indications for intervention in patients of pediatric age (before age 15-16 y) should be exceptional.

2 Evidence of severe stenosis by IVUS quantification is generally essential for a conclusive diagnosis of stenotic severity. Alternatively, we only consider a history of SCA or aborted SCD to be the only factor that by itself could justify intervention in patients with ACAOS-IM of any IVUS-proven anatomic severity. Consistently, stent angioplasty performed by expert operators can obtain full resolution of stenosis and functional success as well as appropriate surgical intervention can. The general abolishment of symptoms is reasonable confirmation of the effectiveness of revascularization intervention and the correctness of our pathophysiological theory (that severe stenosis causes symptoms that disappear after successful recanalization) [2,3], but eventually large series of cases in multicenter controlled studies should be organized according to well-planned protocols.

3 At expert centers, regarding PCI as an alternative to surgical treatment (which is an American Heart Association Class 2 indication), the only PCI contraindication we know of is age of less than 30 years [2,3,5], because of commonly accepted but still unsubstantiated doubts about long-term (ie, 50-year) stent-angioplasty durability. In the R-ACAOS-IM indication, stents did not show any tendency to undergo structural changes (crushing) with aging, and restenosis was rare, as illustrated in Fig. 3 (and, when it occurs, is always the result of fibro-cellular hyperplasia during the first postoperative year) was rare (Fig. 3).

4 More specifically, stent treatment and surgery are still experimental methods of preventing SCD. (There are no objective, randomized studies of surgery versus stenting for R-ACAOS-IM vs medical treatment or disqualification from sports activities and continued medical treatment.) The more than 50 IVUS-confirmed cases of R-ACAOS-IM PCI currently completed at our center in 20 years have been successful at mid-term (at least 5 y), with no mortality (Fig. 3) [2]. During up to 20 years of follow-up, in our experience no patient has died or had an acute infarct, and only one patient required surgery to correct a recurrent restenosis case after PCI. (This failure occurred in a rare case treated with a drug-eluting stent, having joint origination of the LCA and RCA off a single ostium at the left sinus; the stent had to cover the ostial stenosis.) Generally, the in-stent restenosis rate seems to be less than 5% when drug-eluting stents are used, and balloon angioplasty is usually adequate treatment for restenosis [2]. Bare-stent PCI seems to have a much higher restenosis rate and was abandoned after the first 2 years of initial experience. Drawing definitive conclu-

Fig. 2. Histologic (hematoxylin & eosin; A, C) and gross anatomy images (B), all obtained by autopsy in 2 cases of sudden cardiac death in young patients. A) A 17-year-old male victim of sudden cardiac death (SCD) during a basketball game. The typical intramural course of the right coronary artery is shown (R-ACAOS-IM), with apparent moderate lateral compression inside the aortic wall. (This image in autopsy corresponds to IVUS imaging in diastole.) (Panel A image reproduced from Angelini P. Coronary artery anomalies–current clinical issues: definitions, classification, incidence, clinical relevance, and treatment guidelines. Tex Heart Inst J. 2002;29:271-8, with permission.) B and C) A 14-year-old female victim of SCA (complicated by secondary decerebration), which occurred during leisure jogging. Critical stenosis in L-ACAOS-IM was located at the *distal kinked exit* off the intramural segment, on the adventitial side of the aorta. This mechanism of stenosis is rare (as seen in approximately 10-20% of cases of L-ACAOS-IM). A similar clinical case of L-ACAOS-IM with distal stenosis is shown in Fig. 4. (Panel B and C images reproduced from Angelini P. Novel imaging of coronary artery anomalies to assess their prevalence, the causes of clinical symptoms, and the risk of sudden cardiac death. Circ Cardiovasc Imaging. 2014;7:747-54, with permission).

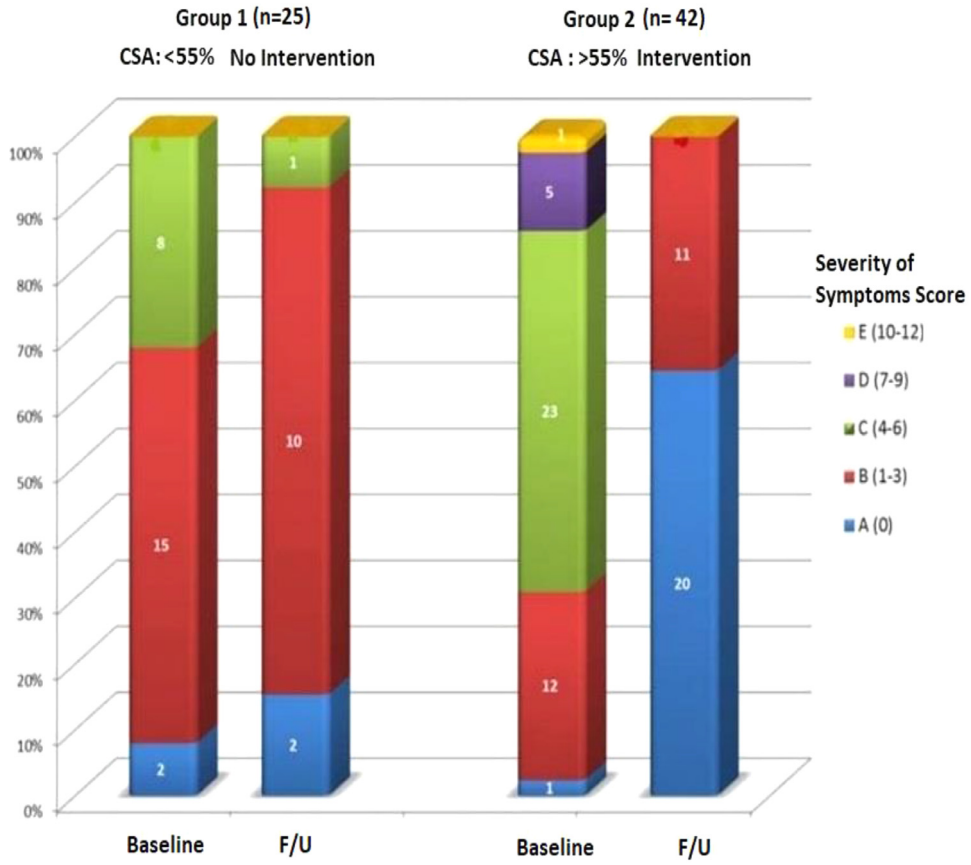


Fig. 3. The percentage of baseline cross-sectional area (CSA) of stenosis stratified by the severity of related symptoms in a continuous series of 67 patients: <55% at baseline (in the 2 left-sided columns) versus >55% CSA stenosis (right columns) treated medically (left) or with PCI (right), in a continuous series of adult patients studied by IVUS imaging because of suspicious symptoms, stress testing, or CTA, after being qualitatively diagnosed with R-ACAOS-IM. Both groups were followed up for a mean of 5 years (range: 2 to 12 years), and there was no mortality in either group. (Adapted from Angelini P, Uribe C, Monge J, Tobis JM, Elayda MA, Willerson JT. Origin of the right coronary artery from the opposite sinus of Valsalva in adults: characterization by intravascular ultrasonography at baseline and after stent angioplasty. Catheter Cardiovasc Interv 2015;86:199-208, modified for clarity and with permission). The 2 columns on the left represent the patients with baseline CSA *stenosis <55% at rest and in diastole*, accompanied by their respective symptomatic state (scores on the right side as % of each category) and followed for 5 years. At 5-year follow-up, the medical-treatment group maintained mild and stable symptoms. In the stent group, symptomatic state was much more severe at baseline but improved substantially after successful PCI intervention. Functional status was classified by the Texas Heart Institute system [3] and varied from asymptomatic (score zero, A) to very severe, like syncope with fall during exertion with spontaneous recovery (score 10-12, E). Globally, the experience showed a definite correlation between severity of stenosis and symptom severity. Of 4 patients in the initial series of PCI who had bare-metal stents (BMS), 2 had restenosis (50%). Of the 38 patients who had drug-eluting stents (DES), 2 had restenosis (5.2%), and one of these had limited-thoracotomy off-pump coronary mammary artery grafting for re-restenosis.

sions about outcomes will require larger, multicenter, prospective studies with accurate long-term follow-up and cardiac mortality data.

5 The most commonly used surgical alternative to PCI in the United States is unroofing [13–15], which requires open-chest extracorporeal circulation and should be carried out by a pediatric cardiovascular surgeon of extensive experience (because this is an unusual and delicate procedure for general adult cardiovascular surgeons). At our center, neo-ostium creation at the end of the IM tract was also used successfully. In Europe, reimplanting the ectopic artery (the distal segment to the intramural initial tract) into the “proper” sinus is more frequently done (and requires great experience, especially when performed in children) [29]. Mammary artery bypass has the substantial limitation of competitive flow with frequent early graft degeneration, unless the proximal native artery is ligated (potentially an excessive price to pay). In small children, the mammary artery is usually small, delicate, and generally recognized to be prone to perioperative coronary arterial spasm. Vein grafting is not an attractive alternative, especially in young patients, for whom graft degeneration and clotting are likely to occur within a few years because of competitive flow in non-critical stenosis at rest (most of R-ACAOS-IM cases).

Details of PCI technique

Specific adaptations of general PCI techniques need to be learned by new operators with experienced proctors, IVUS data, and dedicated guiding catheters, always allowing for stent deployment without initial balloon angioplasty (Fig. 6) [2,3,5,20]. Regarding the length of the IM segment and the site of severest narrowing, the IVUS-proven length of the affected R-ACAOS-IM segment (as evidenced by ovaloid lumen on IVUS, progressing in degree of lateral compression stenosis until the aortic ostium) is consistently about 10 mm (range, 8-12 mm) [2], and the maximal stenosis is localized to the ostial segment, less than 3 mm long, where the arterial lumen becomes flattened (Fig. 7, Videos S1 and S2); that site has maximal, significant systolic obstruction that is liable to further worsening during maximal exercise. The current recommendation is generally to aim at using only one stent per case that can cover the full extent of the IM course [3]. The IM segment is made of aortic wall covered by coronary endothelium (Fig. 2C), and no intimal cholesterol or medial calcium deposits are present, even in the oldest patients, who may have only distal atherosclerotic changes. The issue of potential stent crushing over the years could easily be studied by simple fluoroscopy in proper projection (aligned with the stent), usually without catheterization. Resteno-

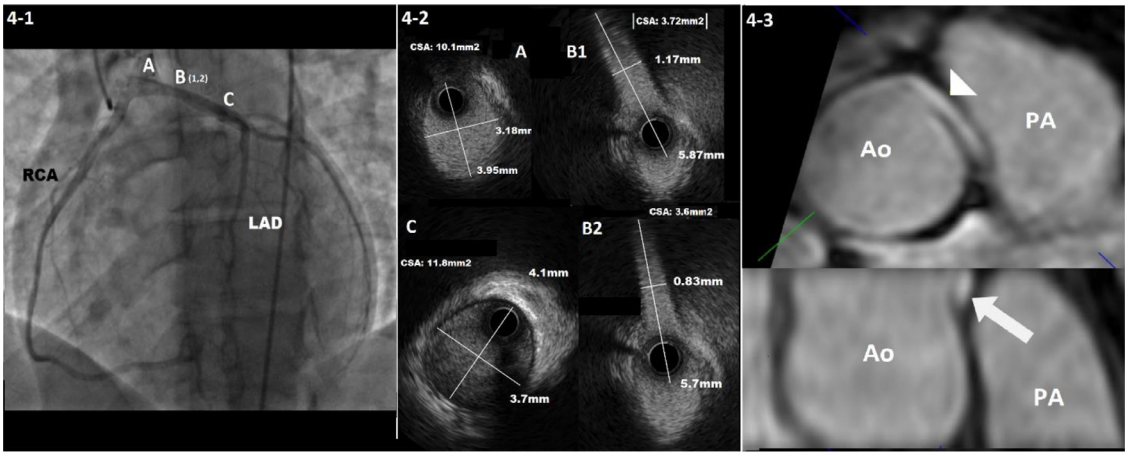


Fig. 4. Coronary angiographic still image (4-1), IVUS imaging (4-2), and MRI (4-3) obtained from a 25-year-old man who had a syncopal spell with prolonged chest pain/troponin elevation while sitting down during an academic test at his university. He survived an emergency left main coronary unroofing operation. (Panels 4-1 and 4-2 were reproduced from Angelini P, Uribe C. Anatomic spectrum of left coronary artery anomalies and associated mechanisms of coronary insufficiency. Catheter Cardiovasc Interv. 2018;92:313-321, with permission.) Note that the angiogram (4-1) shows anomalous origin of the LCA with the normally located RCA (*single short common trunk*), but not its stenosis, which was clearly revealed only by IVUS (4-2, see the severe diastolic and systolic lateral compression in B1 and B2) and, less well, by MRI (4-3, *top* and *bottom*). Note that the proximal L-ACAOS-IM stenosis (seen in 4-1 C) corresponds to the cross-sectional images in B1 and B2 as well as in 4-3 (*bottom*), whereas the distal extramural LCA ("above") arrowhead is at the same site of the angiographic point 4-1 C. The compressed IM site is positioned at the sinotubular junction (4-2 B and 4-3 *bottom*). The ratio between long and short diameters is 4:1 (indicating severe left main trunk stenosis at end-diastole). This case represents essentially the same type of L-ACAOS-IM shown in the histologic example in Fig. 2B, C. This case was successfully treated with mammary artery grafting.

sis is indicated by the appearance of exercise-related angina and/or dyspnea, with a positive nuclear stress test. (Postoperatively, this could be also pharmaceutical because systolic compression is not an issue.) A 15- to 16-mm stent will suffice in most cases as long as it covers the IM course segment from 1-2 mm proximal to the ostium.

L-ACAOS-IM cases

The types of interventions for L-ACAOS-IM are somewhat different from those of R-ACAOS-IM, especially because the LCA normally provides 60-90% of the blood flow to the left ventricular myocardium; thus, L-ACAOS-IM is more complex and riskier to treat than R-ACAOS-IM (Figs. 2 and 4). Additionally, the clinical manifestations of left main trunk ischemia are much more critical than those of R-ACAOS-IM: angina, dyspnea, syncope, SCA, and SCD are more frequent (even at rest and in older patients, in extreme cases) [2]. The best evidence for L-ACAOS-IM being a more serious condition than R-ACAOS-IM comes from the aforementioned study by Eckart et al [4], who reviewed an experience with military recruits (6.3 million over a 25-y period) and found that out of all types of ACAOS, only L-ACAOS-IM was associated with SCD during a 2-month period of strenuous exercises (and was the cause of 33% of medical deaths). This population had not been screened for CAAs specifically being initially studied only by history and physical (grossly insufficient for the target lesion [19]) in the absence of suspicious symptoms. Most of the CAA-related cases of SCD occurred during exertion (86%) and in patients with no history of exercise-related angina. The need for improved screening was recently discussed in depth [19].

A recent MRI-based screening study of a large general adolescent population established the prevalence of any ACAOS-IM, L-ACAOS-IM, and R-ACAOS-IM as 0.45%, 0.12%, and 0.33%, respectively [1]. A baseline >50% diastolic resting-state stenosis of the left main trunk, as described by IVUS, is considered a credible cause of symptoms and a substantial risk factor for SCD during maximal exertion, as well as an accepted indication for intervention, which until the present time has been surgical in cases of CAD [35] and of L-ACAOS-IM. Suspicious symptoms should constitute the main indication for IVUS, especially in candidates for

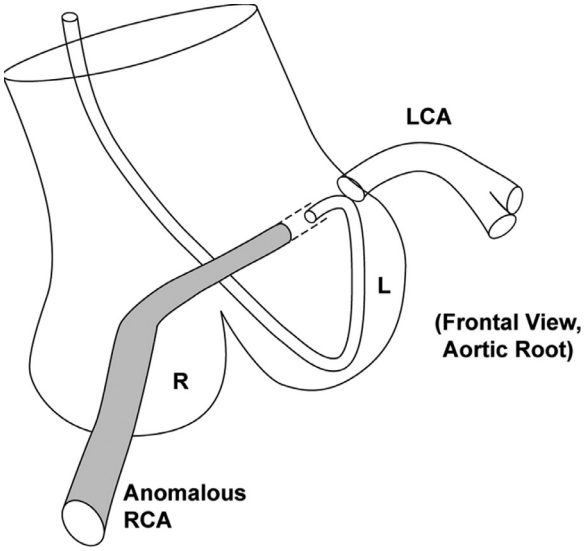


Fig. 5. A schematic representation of the new dedicated guiding catheter for R-ACAOS-IM cases. Note that the left Amplatz guiding catheter was modified to add a terminal 90-degree curve to create alignment with the ectopic, tangential anomalous artery to enhance selective access to the ostium and backup support. The intermittent-line proximal right coronary identifies the intramural course.

strenuous exercise activities. We must acknowledge that an additional, variable dynamic factor may exist that could be especially important in patients with increased elasticity of the aortic root (ie, distensibility to pressure rise). In cases of borderline severity, simulated exercise testing during IVUS measurements with the saline/atropine/dobutamine (SAD) test (by administering a 500-cc saline bolus, atropine 0.5 mg, and dobutamine 40 mcg/Kg/min) could be done to include systolic imaging at a heart rate >150/min [2,3]. In our initial pilot experience, the only contraindication to SAD testing of L-ACAOS-IM was critical stenosis at baseline (>60% CSA stenosis at rest) or a history of SCA/SCD (the main danger is ventricular arrhythmias), but in patients with mild resting stenosis (<50%) it is a safe test.

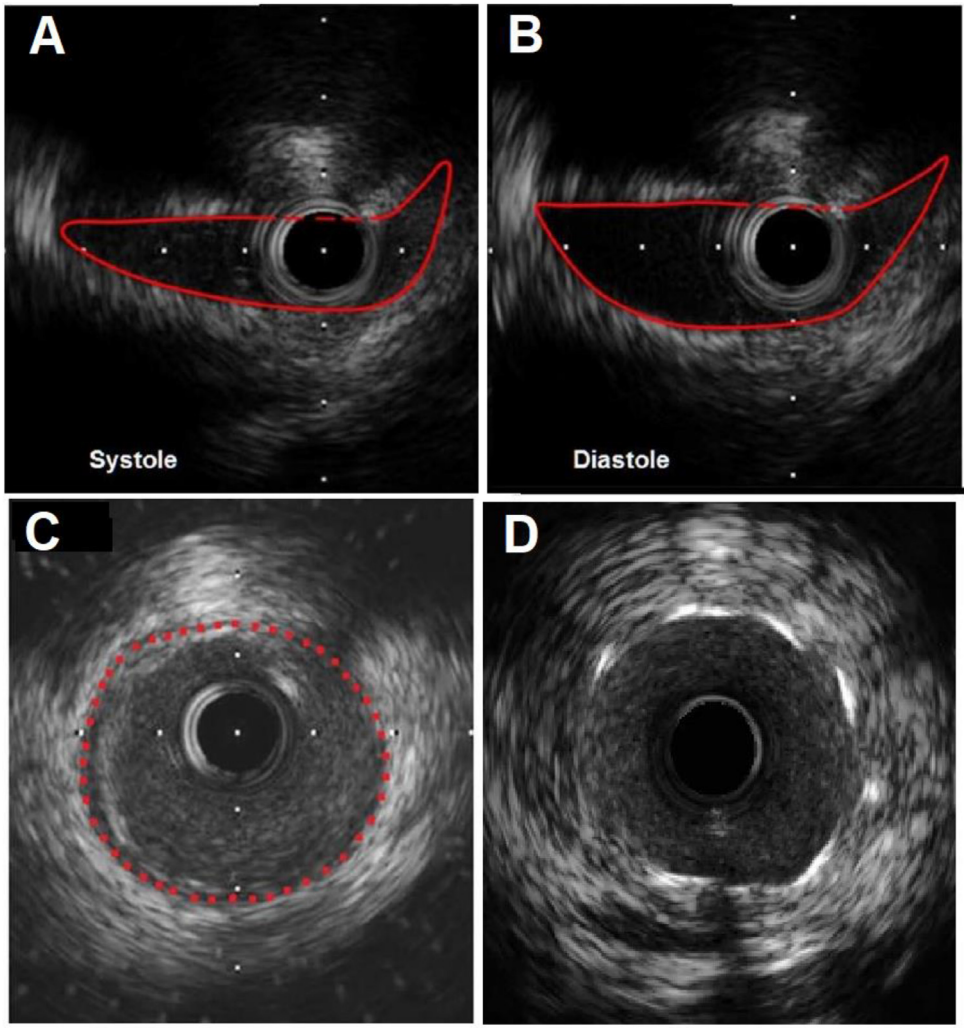


Fig. 6. Angina in a young athlete: IVUS imaging of R-ACAOS-IM in a moderate stenosis case during systole (**A**) and diastole (**B**). (Panels A and B reproduced from Angelini P. Novel imaging of coronary artery anomalies to assess their prevalence, the causes of clinical symptoms, and the risk of sudden cardiac death. Circ Cardiovasc Imaging. 2014;7:747-54, with permission.) When compared to the distal reference cross-section (**C**), the result of stent angioplasty at the IM proximal segment (**D**) is apparent. (Panel C reproduced from Angelini P, Uribe C, Monge J, Tobis JM, Elayda MA, Willerson JT. Origin of the right coronary artery from the opposite sinus of Valsalva in adults: characterization by intravascular ultrasonography at baseline and after stent angioplasty. Catheter Cardiovasc Interv. 2015;86:199-208, with permission.)

Like R-ACAOS-IM, potentially L-ACAOS-IM could be treated effectively with either surgery or stent angioplasty, but adequate evidence of operative safety and long-term effectiveness is still lacking, especially with stenting. Technically, extreme cases should be considered, such as the case of joint origin of RCA and LCA from the same common trunk and the one of ostial stenosis at exit from the IM segment. Currently, the established and uncontested first choice is surgery, mainly by unroofing the IM section, by neo-ostial creation in the left sinus (distal to the stenosis), or by translocating the poststenotic left main coronary into the left sinus of Valsalva [15,17,29]. Careful long-term postoperative follow-up is rarely available even after surgery, but it is essential for reassuring all members of the team (patients, families, professionals) after this still-experimental treatment is applied [13–15]. Postoperative testing by IVUS imaging may be required in occasional cases.

An initial small series of stent angioplasties in L-ACAOS-IM (by a cautious and selective approach but empirical techniques) produced early favorable results in sporadic reports [2], but only a few cases have been precisely reported so far. There are several difficulties to be considered in PCI for L-ACAOS-IM, besides the limited availability of results from current experience. The encouraging late results of R-ACAOS-IM stenting have recently increased interest in starting dedicated multicenter prospective studies at centers of excellence in PCI treatment. The exact location and extent of narrowing must be identified precisely, and only IVUS can accurately describe the anatomy of the left main trunk in L-ACAOS-IM. As stated above, the worst stenosis is sometimes found, not at the ostium (more frequently), but at the distal exit off the IM segment (Figs. 2 and 4). Importantly, even invasive coronary artery angiography may not provide an accurate description of the issues (exact location and severity). The bifurcation of the left main trunk is not usually involved in the IM course and should not be covered by the stent. In cases of a common coronary single trunk, the left main usually becomes IM, not at the common coronary trunk at the aortic ostium or trunk bifurcation, but only after a short extramural left main segment [2]. When the left coronary originates directly from the right sinus of Valsalva, the ostium is frequently slit-like and tangential to the aortic wall. A dedicated guiding catheter with a built-in distal tilt [30] could be uniquely helpful in improving selective engagement, co-axiality, and backup support, as it is in cases of R-ACAOS-IM. (Such a catheter is being developed at our center as a custom-made device.) Stenosis recurrence is probably rare after L-ACAOS-IM stenting, but the risks it poses are more serious than those of R-ACAOS-IM restenosis, including the possibil-

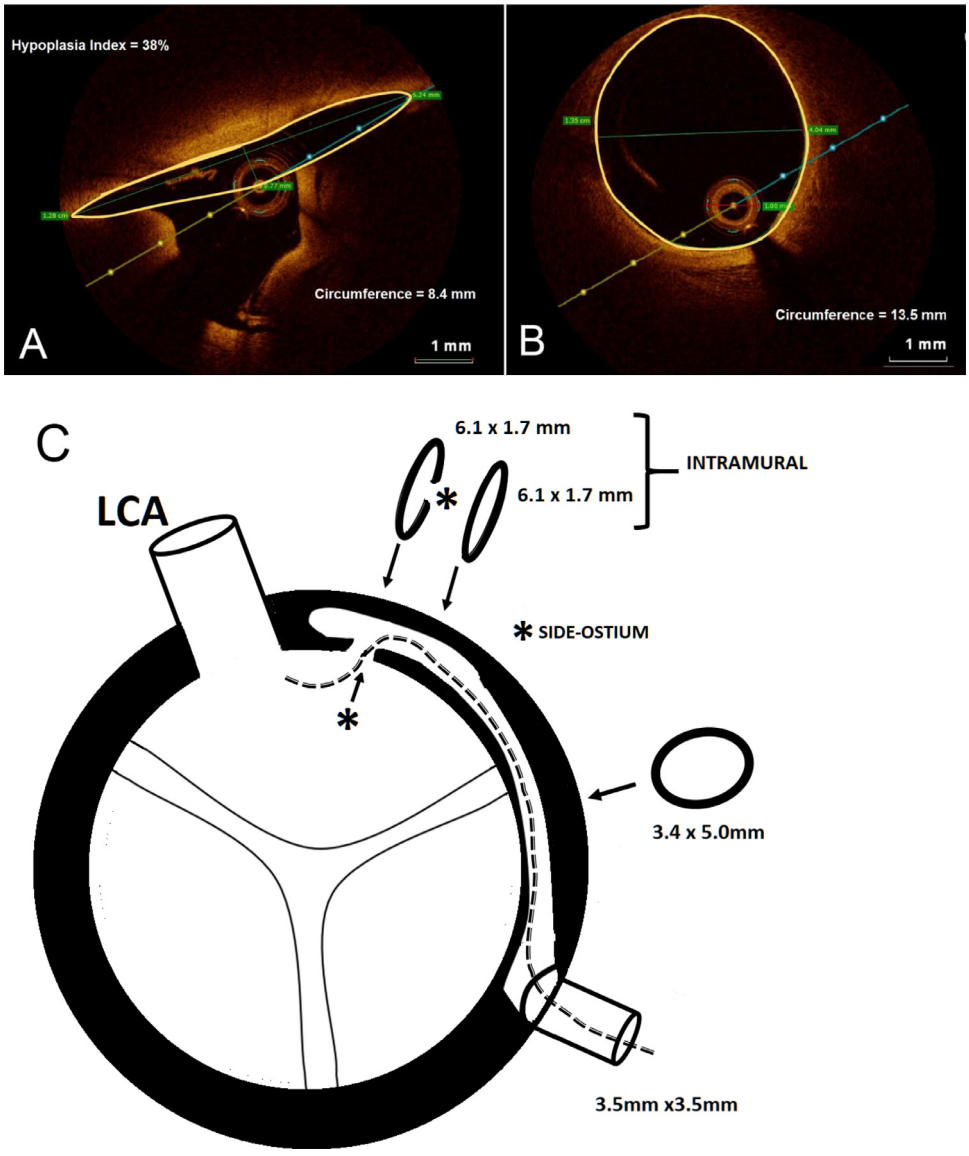


Fig. 7. Still images (A, systole) and (B, distal reference), with video (Video S3) showing optical coherence tomography imaging of a case of severe R-ACAOS-IM. Note that the luminography is very sharp, while the wall thickness and the stereotactic relationships with neighboring structures are not (the pulmonary and aortic walls/lumens are not visible on OCT, but they are on IVUS). C) This is a diagrammatic rendition derived from the OCT images in panel A, and it represents a cross-sectional image of the proximal R-ACAOS-IM, to indicate the detailed anatomy of the initial intramural segment: In this case, the opening of the vessel into the aorta is not from the proximal end of the vessel but from a side defect (the incidence of which we do not yet know). The potential implication is that proximal stenosis in R-ACAOS-IM could be both by lateral compression and the size of the side opening. This detailed anatomic feature only implies that in cases treated with stenting, the stent should cover both the laterally compressed vessel and the very opening into the aorta. Imaging the ostium by OCT is always difficult because of the critical need to deliver selective contrast while also keeping the guiding catheter away from the ostium. If the guiding catheter enters the ostium, it sometimes creates potential for an artifact by enlarging the lumen. Note that the circumference of the proximal R-ACAOS-IM has hypoplasia, with respect to the distal reference circumference (38% smaller). See Video S4, from the same case. The luminal cross-sectional area (CSA) stenosis is 73% in systole at rest (CSA at ostium: 7.82 mm^2; CSA at distal reference vessel: 30.19 mm^2).

ity of SCD as the first clinical manifestation. Close, reliable follow-up will be required.

The surgical technical options are similar to those for R-ACAOS-IM, but in particular we must discuss a limitation of unroofing, the technique most frequently used in the US. It is likely that progressive aortic insufficiency after unroofing is related to progressive enlargement of the aortic anulus because of a weakened aortic wall related to unroofing (which eliminates the inner half of its preoperative medial thickness, below the edge of the anterior commissure of the aortic valve). However, aortic aneurysm formation has never been reported at this site. In the Congenital Heart Surgeons' Society study, 10% of patients needed early redo surgery for ostial stenotic recurrence [14]. Relocating the coronary ostium essentially implies removing the proximal stenotic IM section, which may be problematic in the distal stenosis L-ACAOS-IM cases (Fig. 4). When surgery is done in small children, one should keep in mind also the possibility that the neo-ostium may result too small before the time the patient reaches adulthood. Coronary artery bypass grafting has the same limitations as in R-ACAOS-IM. Most probably, "correcting IAC" in the absence of IM course is an erroneous procedure, as discussed above (referring to L-ACAOS-IS). IVUS imaging has clearly shown that this anomaly does not have either a scissor effect (lateral compression between the aorta and pulmonary artery) or intramural ostial origin from the aortic root, but this is frequently not easy to confirm, even by CTA [3,4,17,20,25,30].

Coronary spasm and CCA

Some cases of non-IM ACAOS have been discovered to be associated with an increased proneness to spontaneous coronary spasm

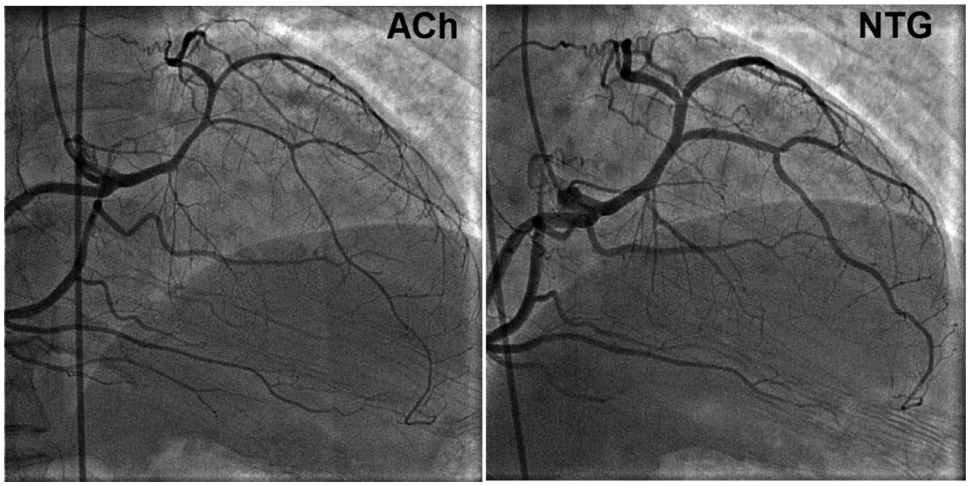


Fig. 8. A 56-year-old woman with recurrent spells of prolonged chest pain and progressive symptoms of congestive heart failure was referred to our center to determine whether her "high-risk L-ACAOS" was intramural (as the referring physician described it) and needed surgery on the basis of CTA findings. Her left ventricular ejection fraction was initially 35%. Coronary angiography clearly shows a case of L-ACAOS-IS featuring a single ostium at the right sinus of Valsalva, with typical anterior (not IM, pre-aortic) initial course and later infundibular course, without resting coronary stenosis. Administering intracoronary ACh revealed severe and diffuse coronary narrowing (left panel), which was quickly resolved by intracoronary administration of nitroglycerin (right panel). Note that *all* small branches, even atrial and septal branches, are severely narrowed by ACh administration. After long-term calcium antagonist and nitroglycerine therapy, angina almost completely disappeared and left ventricular function improved to 40-45%. We interpreted the case as one of sustained spontaneous spastic episodes, inducing myocardial stunning (no evidence of scar was noticed on late gadolinium enhancement MRI). Note the presence of the first septal branch off the undivided left main coronary artery, which indicates the start of the intraseptal course. (Reproduced from Angelini P, Uribe C. Anatomic spectrum of LCA anomalies and associated mechanisms of coronary insufficiency. Catheter Cardiovasc Interv. 2018;92:313-321, with permission.)

with clinical resting angina (Fig. 3) [2]. The optimal technique for objectively recognizing such spasm is generically by acetylcholine test of endothelial dysfunction. In our Center for Coronary Artery Anomalies at the Texas Heart Institute, we have documented several similar cases. In some examples, sustained spontaneous spasm events may lead to myocardial stunning or, in patients with recurrent/prolonged episodes, subacute, transient, or permanent ischemic scarring and cardiomyopathy [2]. Additionally, we have observed cases of ACAOS associated with positive ACh testing in patients with the following types of ACAOS: IS (most frequently), RA, PP, and rarely IM (only distal to the IM proximal section). Typically, spontaneous symptomatic episodes of angina occur at middle-to-older age, in both male and female carriers. The peculiar feature of these cases is that increased spasticity is most frequently diffuse, and not localized at coronary proximal segments like in Prinzmetal angina. The reason for the association between spasm and ACAOS is unclear, but it may relate to the abnormal cardiac innervation of these abnormal-course arteries. Nitroglycerine quickly resolves ACh-induced spasm, as well as clinical episodes. Calcium antagonists are definitely effective in preventing spasm (as we observed during ACh testing in 15 patients in our empirical experience), but the experience is small. Surgical intervention is not routinely required [24]. Progression to irreversible terminal cardiomyopathy is apparently rare but is frequently unrecognized.

Conclusions

Coronary artery anomalies are a complex and evolving field in cardiology. At this stage of our learning process, we should realize that 3 different categories of anomalies exist: 1) ACAOS that represents the body's natural effort to adapt to embryologic developmental anatomic but not functional defects, like in the PP, IS, and RA variants. 2) Apparently, a longer-than-normal proximal coronary trunk does not necessarily imply by itself coronary dysfunction. 3) At the opposite end of the spectrum, some anomalous anatomic patterns (perhaps 10-20% of all types, eg, ACAOS-IM) are potentially capable of causing serious clinical consequences because they feature severe degrees of fixed and dynamic stenosis, which require careful quantification (frequently by IVUS imaging at rest and with simulated exercise). Those can be potentially treated safely and successfully with stents or surgery at expert centers, if identified in a timely fashion. 4) Many different anatomic patterns of ACAOS are occasionally accompanied by coronary spontaneous spasm in adults (manifesting as resting angina that is responsive to nitrates or calcium blockers, probably in 5-25% of cases).

We need to be aware of this wide spectrum and of the persistently unsettled questions about indications for advanced evaluation of severity or interventions, and about optimal techniques, while dedicated centers of excellence should urgently join collaborative multicenter, coordinated, prospective studies [5,9,14,19]. If one considers that 0.45% of the population is born with some kind of ACAOS-IM, about 1,300,000 children and adults in the United States probably have one, implying the need for a specific and detailed preventive screening plan for athletes. Documentation of effective prevention will be necessary and only possible by large prospective studies with accurate screening in persons who are following an intense and consistent exercise program, while showing the cause of the eventual SCD with autopsy. This is probably possible only in US military recruits [19].

Current recommendations established by official organizations do not take into consideration the findings of more recent pilot studies of IVUS characterization and stent angioplasty.

Declaration of Competing Interest

None of the authors has any conflict of interest to report.

Acknowledgments

The authors thank Stephen N. Palmer, PhD, ELS, of the Department of Scientific Publications at the Texas Heart Institute for his important editorial contributions.

Funding

None.

Disclosures

None of the authors has any conflict of interest to report.

Ethical-Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2022.05.007.

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