JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 4, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2017.02.004

Multimodality Imaging in Individuals With Anomalous Coronary Arteries

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ABSTRACT

Anomalous coronary arteries (ACA) represent a congenital disorder with an anomalous location of the coronary ostium and/or vascular course. Although most individuals with ACA are asymptomatic and remain undiagnosed, some ACA variants are clinically significant leading to symptoms and even adverse cardiac events. Currently, disease prevalence, pathophysiological mechanisms, risks of sudden cardiac death, and the optimal assessment and treatment strategies among subtypes of ACA remain largely unknown. Consequently, there is a lack of guidelines regarding imaging, sport restriction, and treatment options in individuals with ACA at all ages. Cardiac imaging techniques may play a pivotal role in the assessment of individuals with ACA and may offer guidance toward an optimal treatment strategy. This state-of-the-art review highlights current challenges and future perspectives with a special focus on the role of noninvasive multimodality imaging in patients with ACA. (J Am Coll Cardiol Img 2017;10:471–81)
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Anomalous coronary arteries (ACA) represent a congenital disorder hallmarked by an anomalous location of the coronary ostium and/or vessel course. The prevalence of ACA in the general population is estimated at 1% (1-4). Most patients with ACA remain undiagnosed because of a lack of symptoms, but a minority becomes symptomatic and experiences adverse cardiac events. Interarterial course (IAC), slit-like ostium, intramural course, acute take-off angle with tangential vessel course, and proximal narrowing of the anomalous vessel are considered high-risk anatomic features (**Central Illustration**) that have been associated with an increased risk of myocardial ischemia, ventricular arrhythmias, heart failure, and sudden cardiac death (SCD) (5-9). Patients with these features are at a higher risk for SCD when engaged in strenuous exertion (5-9). Autopsy series showed that, after hypertrophic cardiomyopathy, ACA is the second most common cause of sports-related SCD in young athletes during or shortly after strenuous exercise and accounts for up to one-third of SCD in military recruits in the United States (10,11). However, some reports had suggested that such risk of SCD was overestimated because of reporting bias from those presented with a fatal event (12,13). A more accurate representation of the risk of SCD has been hampered by a lack of mandatory reporting of SCD in most countries, inconsistencies in conduction of autopsy, and variable methods used to verify the cause of death.

Besides young athletes with ACA, substantial interest has emerged in older patients with this condition. With increased use of noninvasive imaging in evaluation of coronary artery disease (CAD) in middle-aged and older individuals, an increase in incidental ACA can be expected. Given a lack of evidence-based guidelines in recommending optimal diagnostic strategies, sports restriction, and treatment options in patients with ACA, cardiologists, cardiac imaging specialists, and cardiac surgeons are often ill-equipped in counselling their patients. At present, recommendations are limited and inconsistent, ranging from an immediate surgical approach to watchful waiting with sports restriction. Cardiac imaging of ACA may offer additional information

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Dr. Gräni has received funding support from the Novartis Foundation for Medical-Biological Research, Bangerter-Rhyner Foundation, Swiss Sports Medicine Society, and Kreislauf Kardiologie Foundation. Dr. Kwong has received research support from the National Institutes of Health (1UH2 TR000901, 1RO1DK083424-01, and 1U01HL117006), Alnylam Pharmaceuticals, and the Society for the Cardiovascular Magnetic Resonance. The University Hospital of Zurich holds a research contract with GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 19, 2016; revised manuscript received February 8, 2017, accepted February 15, 2017.

JACC: CARDIOVASCULAR IMAGING, VOL. 10, NO. 4, 2017
APRIL 2017:471–81

ABBREVIATIONS AND ACRONYMS

ACA = anomalous coronary arteries

ACAOS = anomalous coronary arteries of the opposite sinus of Valsalva

CAD = coronary artery disease

CMR = cardiac magnetic resonance imaging

CTA = computed tomography angiography

IAC = interarterial course

MPI = myocardial perfusion imaging

PET = positron emission tomography

SCD = sudden cardiac death

SPECT = single-photon emission computed tomography

TTE = transthoracic echocardiography

needed for decision-making and guidance of optimal treatments.

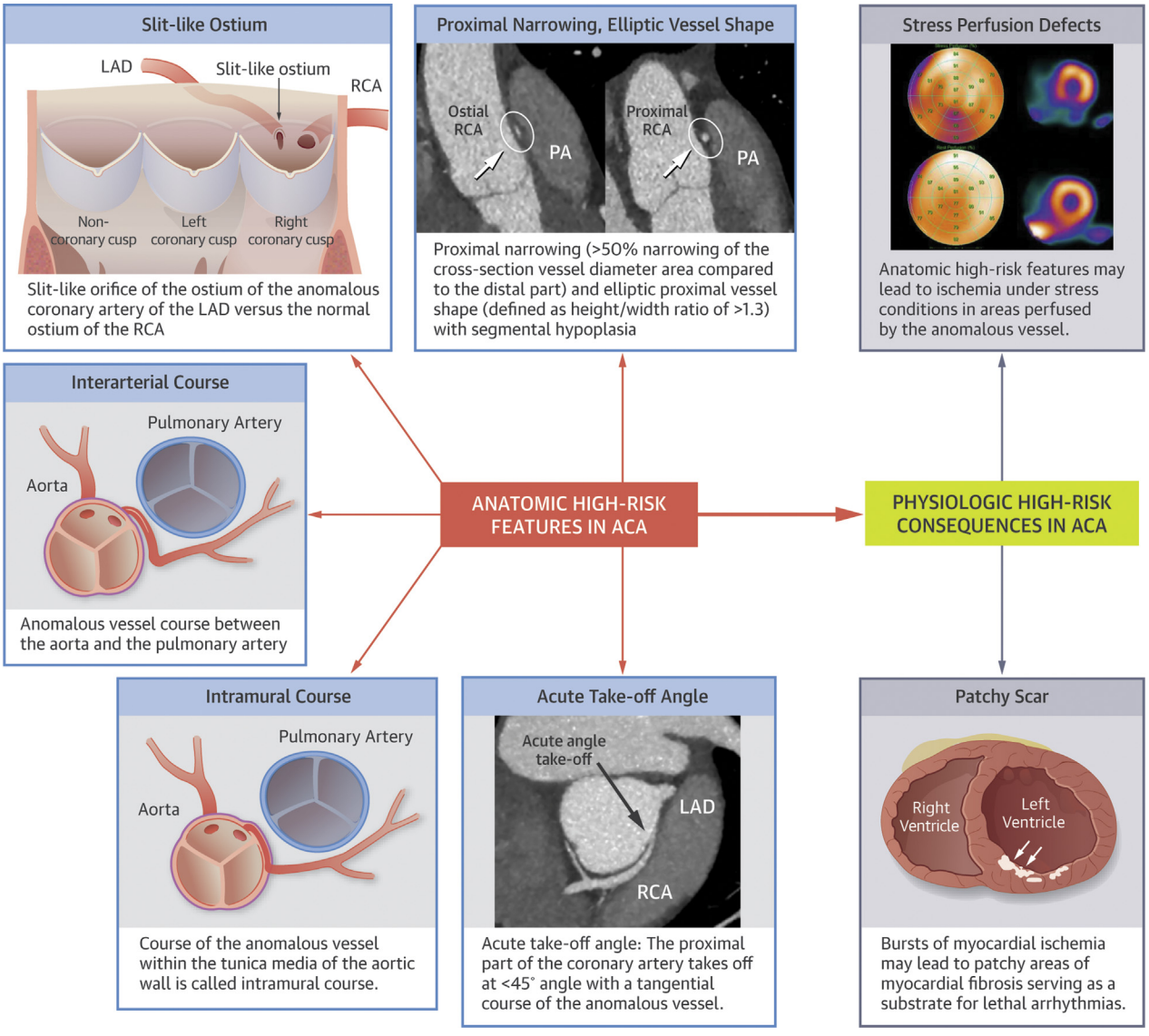
CHALLENGES IN CHARACTERIZING ACA

The coronary arteries were historically considered to be embryological outgrowths of the aortic root. However, more than 3 decades of evidence had suggested that coronary endothelial precursors self-organize in the subepicardial space and form a vascular plexus that only in later stages of embryological development connects to the aorta (14). The underlying mechanism of ACA evolvement remains largely unknown. Some evidence exists that genes (e.g., Tbx1 gene), coronary arteriovenous growth coordination, aortic root and CXCL12/CXCR4 signaling axis, vascular density around the aortic trunk, modulated by hypoxic domains and local vascular endothelial growth factor availability are involved in the correct connection between the distal coronary artery parts and the proximal aortic root parts (4). One of the clinically important ACA variants, namely ACA of the opposite sinus of Valsalva (ACAOS), is divided into right-ACAOS (anomalous right coronary vessel originating from the left coronary sinus) and left-ACAOS (the anomalous left coronary artery originates from the right coronary sinus). Right-ACAOS are more prevalent than left-ACAOS (15), but it has been reported that only left-ACAOS may lead to SCD, given the much larger amount of myocardium it supplies (16). However, SCD occurrence in patients with right-ACAOS has been reported (4,17), specifically those with an IAC between the aorta and the pulmonary artery, which is considered a "malignant" variant given the potential of extracoronary compression by the adjacent great arteries. On the contrary, an anomalous course between the right ventricular outflow tract and the aorta (also known as subpulmonic or intraseptal course) is not considered malignant and is usually not associated with high-risk anatomic features, such as a slit-like ostium (18). A retroaortal (i.e., between the left atrium and behind the aorta) or pre-pulmonal (i.e., ventral of the pulmonary artery) course of the anomalous vessels and those originating from the noncoronary sinus are considered benign variants (19). Aside from IAC and the slit-like ostium, other proposed high-risk anatomic features include an acute take-off angle (<45°) with a tangential course of the anomalous vessel, an intramural course (of the anomalous vessel within the tunica media of the aortic wall), an elliptic luminal vessel shape (defined as height/width ratio of >1.3), and proximal vessel narrowing (hypoplasia) of the anomalous vessels (>50% narrowing of the cross-section vessel area compared to the distal part) (20–22).

Besides great vessel compression of the ACA based primarily on anecdotal evidence, other hypotheses regarding the underlying mechanism of SCD in patients with ACA exist. Increased cardiac output during exercise may cause valve-like obstruction of the slit-like ostium because of vessel expansion, and coronary flow is further impeded if acute angulation of the arterial take-off coexists. However, with increased pressure and volume during systole, associated aortic dilation and torsion may lead to asymmetrical lateral compression of the proximal and narrowed intramural vessel segments (4,5,23). Strenuous physical exercise, which results in shortened diastolic filling time and tachycardia, could lead to ischemia and arrhythmia. Whether coronary spasm may play an additional aggravating role is unclear. Others proposed that restriction of flow through the relatively noncompliant commissural area of the anomalous vessel originating from the opposite coronary cusp may be a contributing factor (24–26). Supported by limited clinical evidence at present, another hypothesis includes repetitive myocardial ischemia leading to cumulative patchy fibrosis, serving as a substrate for lethal arrhythmias (4,6,27).

Several ACA morphologies are considered clinically benign: these include high take-off of coronary arteries from the aorta, duplication of coronary arteries, absent left main stem with separate ostium for left anterior descending coronary artery and left circumflex coronary artery (5), or intramyocardial course (myocardial bridges) of the epicardial portion of the coronary artery (3). A very rare but mostly lethal coronary anomaly presenting primarily in early infancy is the anomalous origin of the coronary artery from the pulmonary artery (also called Bland-White-Garland syndrome) (28). In this anomaly, extensive collaterals develop between the right and left coronary arterial systems and over time the flow reverses causing myocardial ischemia and congestive heart failure (28). Because ACA with anatomic high-risk features is believed to confer a greater risk for adverse cardiac events, exact anatomic depiction as offered by multimodality noninvasive imaging may be helpful for further risk stratification (10,29–32). In the rest of this review, we focus on the more common variants of ACAOS.

CENTRAL ILLUSTRATION **Anatomic High-Risk Features and Physiologic High-Risk Consequences of ACA**



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The different anatomic high-risk features, such as interarterial course, slit-like ostium, acute take-off angle, intramural course, elliptic vessel shape, and proximal vessel narrowing of the anomalous vessels of patients with anomalous coronary arteries (ACA) are shown. Possible underlying mechanism in patients with anatomic high-risk features may lead to physiologic high-risk consequences, such as myocardial perfusion defect and myocardial scar. Increased cardiac output during exercise may on one hand cause valve-like obstruction of the slit-like ostium due to vessel expansion, and coronary flow is further impeded if acute angulation of the arterial take-off co-exists. On the other hand, with increased pressure and volume during systole, associated aortic dilation and torsion may lead to asymmetrical lateral compression of the proximal and narrowed intramural, elliptic vessel segments. Strenuous physical exercise, which results in shortened diastolic filling time and tachycardia could lead to ischemia and arrhythmia. Coronary spasm may play an additional aggravating role. Restriction of flow through the relatively noncompliant commissural area of the anomalous vessel originating from the opposite coronary cusp may be a contributing factor. Repetitive myocardial ischemia may lead to patchy fibrosis, serving as a substrate for lethal arrhythmias. LAD = left anterior descending artery; PA = pulmonary artery; RCA = right coronary artery.

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TABLE 1 Different Imaging Modalities in Evaluating Anomalous Coronary Arteries

	TTE	TEE	Coronary CTA	CMR	Invasive Angiography and IVUS	SPECT	PET
Spatial resolution	++	++	+++	++	++++	+	+
Temporal resolution	++	+++	++	++	+++	+	+
Anatomy of coronary arteries							
Proximal	+++	+++	++++	++++	+++	-	-
Distal	+	+	++++	++	+++	-	-
Anatomic high-risk features in anomalous coronary arteries							
Interarterial course	++	++	++++	++++	++	-	-
Slit-like ostium	+	+	++++	++	+++	-	-
Take-off angle	++	+	++++	++++	+	-	-
Intramural course	++	++	++++	+++	++++	-	-
Proximal narrowing	++	++	+++	++	+++	-	-
Elliptic shape	++	++	+++	++	+++	-	-
Physiologic high-risk consequences in anomalous coronary arteries							
Ischemia	++	-	-	++++	++	++++	++++
Scar	+	+	++	++++	-	+++	+++
Feasibility in children	++++	++	++	++	++	++	++
Ionizing radiation exposure	-	-	+	-	++	+++	+++
Costs (highly variable in different institutions and countries)	+	++	++	+++	+++	+++	++++

CMR = cardiac magnetic resonance; CTA = computed tomography angiography; IVUS = intravascular ultrasound; PET = positron emission tomography; SPECT = single-photon emission computed tomography; TEE= transesophageal echocardiography; TTE = transthoracic echocardiography.

MULTIMODALITY IMAGING OF ACA

ECHOCARDIOGRAPHY. With transthoracic echocardiography (TTE) origin of ACA and proximal course can be assessed noninvasively with high accuracy and without any radiation exposure (33). One report demonstrated that the coronary ostia can be visualized in 90% and that the identification of anomalous ostia is highly specific if TTE is performed by an experienced sonographer and with good image quality (34,35). TTE can also use color Doppler to demonstrate an intramural course of ACA that might be missed by coronary angiography (**Table 1**) (36,37). On one study of patients with ACA being considered for surgical correction, TTE identified the intramural or extramural course at an accuracy of 92.5% (37). TTE may also assess the functional significance of ACA by evaluating for myocardial ischemia using dobutamine stress test (38). Most children have excellent transthoracic acoustic window, thus TTE is often arguably the most valuable diagnostic tool for ACA in children without the need for additional imaging (2,35,39,40). In adults or those with limited transthoracic acoustic window, TTE is only of limited value (41) and transesophageal echocardiography is more sensitive than TTE in identifying ACA and the associated anatomic high-risk features. Transesophageal echocardiography provides superior sensitivity for assessing the vessel course than TTE (33). However, reports of clinical application of echocardiography in the diagnosis and management of patients with ACA have reduced consistency because of interobserver variability and institutional experiences. In a multicenter study of 159 patients, agreement between participating centers and the "expert" echocardiographic imaging core laboratory was poor (42). It seems obvious that for meaningful clinical adaptation of echocardiography in ACA assessment, standardized protocols must be used for imaging and reporting of echocardiography studies.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY. Given its rapid speed and tomographic depiction of cardiac anatomy in 3D, coronary computed tomography angiography (CTA) has become the first-line imaging modality in most centers to visualize the origin and full course of ACA in adult patients (3,43). Coronary CTA has undergone substantial technical advancements over the last decade, particularly with regard to spatial resolution and reduction of radiation exposure to patients to an average range of 0.21 to 0.5 mSv in daily clinical routine (44,45). Virtual angiographic view of coronary CTA helps to evaluate anatomic high-risk feature, such as the slit-like origin. Double-oblique multiplanar reformatted images can identify other anatomic high-risk features, such as acute take-off angle, intramural and elliptic luminal vessel shape, and proximal vessel narrowing of the anomalous vessel (21,22).

CARDIAC MAGNETIC RESONANCE IMAGING. Similar to coronary CTA, cardiac magnetic resonance (CMR) offers tomographic 3D imaging at high spatial resolution (slightly lower than coronary CTA) allowing visualization of the origin and the full coronary course of ACA, including the relationship of ACA with respect to the great vessels. Furthermore, CMR offers a wealth of additional relevant information including valvular function, ventricular function, regional contractility, and myocardial viability, all of which could be important considerations during the preoperative evaluation or post-operative follow-up in such patients (46–51). Surface-rendered angiographic view of the ostia can be obtained by CMR for the assessment of the anatomic high-risk feature of slit-like origin (50,52). Although contrast administration improves the quality of images, CMR coronary angiography can be done without the use of contrast agents and with its lack of need for ionizing radiation, rendering this modality particularly helpful in pediatric populations. For this reason, the current American Heart Association statement on noninvasive

imaging of coronary arteries in the young recommends CMR over coronary CTA in assessing ACA (53,54). With technical improvement in suppressing respiratory motion, CMR coronary angiography performed at experienced centers can consistently assess the origin, and proximal and mid courses of coronary arteries. However, coronary CTA overall provides a higher diagnostic consistency across imaging centers and may be favored because of a more accurate depiction of the entire anomalous vessel including the distal coronary segments (48,55). In either patient group, because of the specific technical requirements of CMR, local imaging expertise and equipment capability may be relevant factors. Because patchy areas of myocardial fibrosis might occur in patients with ACA, possibly serving as a substrate for lethal arrhythmias (6), CMR can be used to identify myocardial fibrosis, using late enhancement images after gadolinium injection, therefore offering a means for further risk stratification (56). In addition, analogous to dobutamine TTE, dobutamine stress CMR cine and myocardial perfusion imaging (MPI) can be performed to assess the functional relevance of a coronary anomaly during a state of induced increased myocardial oxygen demand.

NUCLEAR CARDIAC IMAGING AND HYBRID IMAGING. Nuclear cardiac imaging modalities play an important role in assessing myocardial perfusion, thus allowing for assessment of the functional relevance of any ACA. Single-photon emission computed tomography (SPECT) MPI and positron emission tomography (PET) MPI may unmask ischemia in asymptomatic and symptomatic patients with ACA. De Luca et al. (57) detected ischemia in patients with ACA with SPECT-MPI in 4 of 5 patients and Uebleis et al. (58) in one-third of 17 patients. By contrast, using hybrid coronary CTA/SPECT-MPI, we recently demonstrated that in middle-aged or older patients, ischemia is mostly caused by concomitant CAD rather than by ACA itself (59). Furthermore, with the use of hybrid coronary CTA/PET-MPI we demonstrated that even in absence of localized perfusion defects, coronary flow reserve was impaired in ACA-supplied territories (60). Therefore, beside the anatomic description of high-risk features, further risk stratification with nuclear perfusion imaging tests and hybrid imaging is warranted, especially in unclear cases (3,58,60).

INVASIVE CORONARY ANGIOGRAPHY. Invasive coronary angiography used to be the first-line imaging modality to asses ACA for decades. Because of its invasiveness, radiation exposure, and inability to characterize noncoronary cardiac anatomy that surrounds ACA, invasive coronary angiography in ACA should only be used to complement a noninvasive imaging-first approach using coronary CTA or CMR. Invasive coronary angiography in combination with intravascular ultrasound and optical coherence tomography with its high spatial resolution of 10 μm may be of value for the assessment of the luminal geometry at the very proximal portion of the ectopic vessels where the identification and assessment of the severity of intramural compression are of importance (15). Furthermore, under dobutamine stress conditions invasive assessment of vessel measurements can be performed. However, because the cross-sectional diameters of the intravascular ultrasound probes (approximately 1 mm) may be too large to permit the assessment of the more severe intramural parts under baseline and exercise conditions, optical coherence tomography (with its smaller diameter catheter) may be more feasible in providing accurate results (15).

CHALLENGES OF FUNCTIONAL IMAGING IN ACA. Although noninvasive (and in some cases invasive) imaging has a high diagnostic and management implications in ACA cases, several questions remain to be elucidated: Which protocols should be used for ischemia testing? Is pharmacological testing using dobutamine or vasodilator an effective alternative to physical stress? Are patients with negative stress test results truly not at risk? How to overcome the issue that the standard vessel territory distribution is not applicable in patients with ACA?

There is no current consensus on the type of stress testing protocol as the most appropriate for the evaluation of myocardial perfusion in patients with ACA. This is in part because of the nonstandardized practice in the choices of selecting protocols used in stress testing. Exercise stress protocols most closely resemble the hemodynamic circumstances during physical activities in everyday life and during sports. However, there is evidence that physical stress tests may yield false negative results because it has been proposed that ischemia in patients with ACA might be intermittent in nature. Brothers et al. (61) have demonstrated a low incidence of ischemia detection in a small number of symptomatic patients with ACA who underwent pre-operative physical stress test. Furthermore, doubts have been raised if the typical exercise target toward an 85% of the predicted maximum heart rate based on a patient's age is appropriate in this setting and patient cohort. It may be reasonable to strive toward achieving substantially higher physical workload beyond the level of standard exercise stress protocols so as to increase the sensitivity of detecting ischemia induced by ACA in

real life conditions. Regarding pharmacological stress testing, it was demonstrated that inotropic stress induced by dobutamine infusion can lead to an anatomic compression of slit-like ostium and changes in the vessel diameter of ACA that can be reliably visualized using intravascular ultrasound imaging (15,62). Thus, it seems that dobutamine stress testing could be used as a valid alternative to physical stress testing (57,62). Whether vasodilation using adenosine might be an alternative for functional evaluation in selected cases remains debatable: Angelini et al. (24) showed normal invasive fractional flow reserve values with adenosine stress in patients with ACA. By contrast, Lim et al. (62) demonstrated that fractional flow reserve in a malignant variant of ACA was similarly reduced by both dobutamine and adenosine.

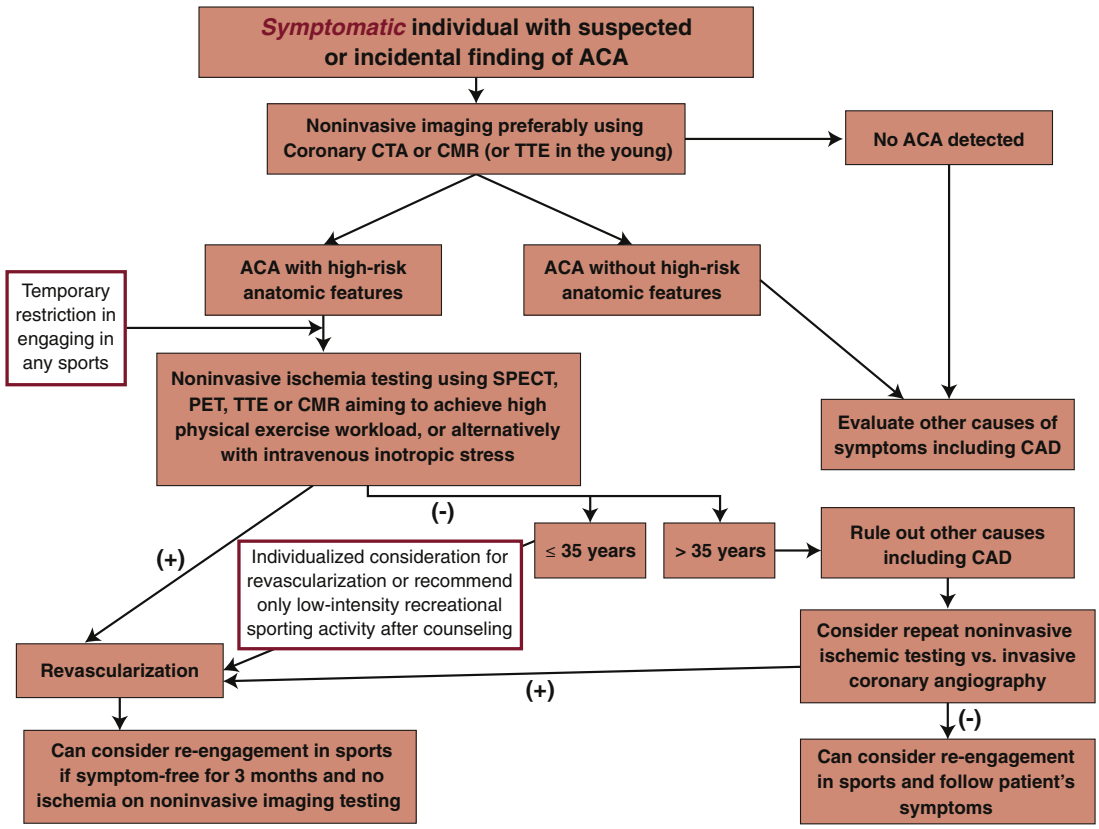
The risk of SCD (6,38) and the potential lethal arrhythmias in patients with ACA remain inadequately addressed at present. Our group and others showed that ACA with IAC are more associated with anatomic high-risk features compared with ACA without IAC (22,59,63). ACA without IAC seem to be less associated with SCD because of the lack of potential dynamic obstruction (37), most likely caused by the absence of other contributing anatomic high-risk features. Another important issue is that the vascular territory distribution based on the American Heart Association segmental nomenclature often is not applicable in patients with ACA and interpretation of noninvasive imaging needs to take this factor into consideration. For example, a negative SPECT-MPI, PET-MPI, or CMR stress perfusion imaging finding in right-ACAOS with left coronary vessel dominance might be falsely negative, because ischemia of the right heart cannot be visualized in this case. One could argue that in this case the myocardium at risk might be relatively small, but arrhythmias could still be provoked. Fused hybrid imaging incorporating a functional and a morphological imaging modality might overcome this issue by correctly allocating the affected vessel to the correct vessel territory, such as through fusion of coronary CTA and SPECT-MPI or PET-MPI (59,60). Finally, it should be mentioned that there is a lack of evidence on the diagnostic accuracies of any functional tests for ischemia detection in ACA and that further studies are needed to finally provide answers to this question.

SPORTS RESTRICTION AND SURGICAL CORRECTION IN ACA

YOUNG INDIVIDUALS (≤35 YEARS OF AGE) WITH ACA. In management of young individuals with ACA, several issues including safety in engaging in sporting activities, screening of athletes, and current indication for surgical correction remain unclear. It has been recommended that athletes with any subtypes of ACA should refrain from engaging in competitive sports (64). Reuptake and participation in sports is only allowed at least 3 months after successful surgical correction of ACA and with myocardial ischemia, ventricular arrhythmia, tachyarrhythmia, or left ventricular dysfunction during maximal exercise testing excluded during follow-up visits (65,66). Gersony (67) had proposed that only left-ACAOS and symptomatic right-ACAOS patients be candidates for surgical correction of ACA. The American College of Cardiology/American Heart Association guidelines for the management of adults with congenital heart disease recommended that individuals younger than 35 years of age with left-ACAOS with coexisting high-risk anatomic feature, such as intramural course, should undergo surgical correction (68). Surgical correction may consist of ectopic coronary reimplantation, unroofing of the anomalous vessel along its intramural segment, and creation of a neo-orifice at the anatomically correct sinus or coronary bypass grafting (26). However, the latter might be less effective and the bypass graft is prone to closure because of competing flow in the native vessel.

The recent American Heart Association/American College of Cardiology Task Force 4 addressed the issue of eligibility and disqualification in competitive athletes with ACA, and made recommendation adaptions regarding restrictions of sporting activities and necessity of surgery among low-risk patients (69). Although the supporting level of evidence is limited given the rarity of ACA and its corresponding medical literature, the following recommendations were made: based on current recommendations, participation in any competitive sport in athletes with left-ACAOS and IAC before surgical correction is considered Class III (Level of Evidence: B). In these patients, current recommendations allow participation in low static or low dynamic class IA sports. These recommendations apply to patients with ACA diagnosed in either intentional or incidental conditions. This recommendation extends also to patients with right-ACAOS with either symptoms or a positive exercise stress test. Regarding right-ACAOS, IAC is not mentioned in the recommendations. In athletes with uncorrected right-ACAOS who exhibit symptoms, arrhythmias, or signs of ischemia on exercise stress test, participation in all competitive sports is also considered Class III (Level of Evidence: C), with the possible exception of Class IA sports, before a surgical repair. For patients with right-ACAOS but

FIGURE 1 Evaluation of "Symptomatic" Individuals With Suspected or Incidental Finding of ACA



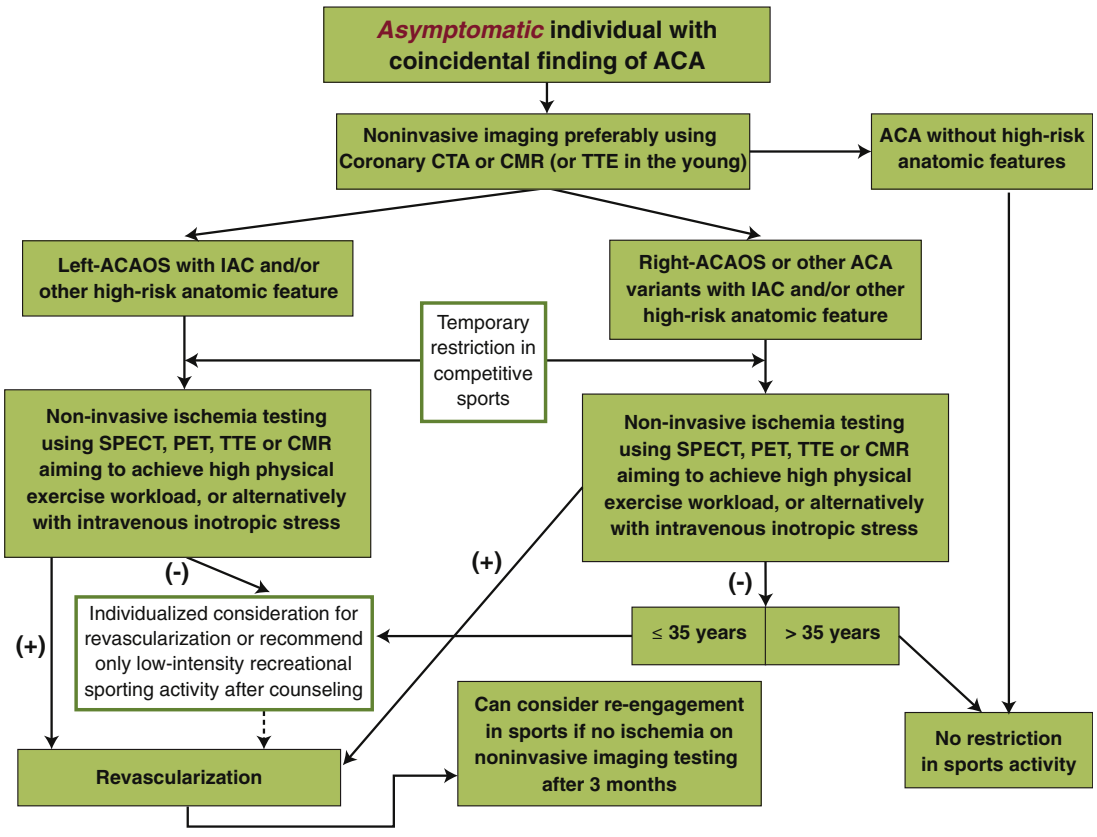
Treatment flow chart for evaluation of "symptomatic" individuals with suspected or incidental finding of anomalous coronary arteries (ACA). CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography; TTE = transthoracic echocardiography.

with no symptoms or ischemia on an adequately performed exercise stress test, participation in competitive sports can be considered after adequate counseling of the athlete or the athlete's parents (Class IIa; Level of Evidence: C) (69). However, other high-risk anatomic features are not incorporated in these recommendations.

MIDDLE-AGED OR OLDER INDIVIDUALS (>35 YEARS OF AGE) WITH ACA. Management of middle-aged or older athletes and nonathletes with symptomatic or incidental ACA finding creates a greater dilemma (61,70). Although similar recommendations compared with younger patients exist (68), to differentiate whether a middle-aged or older individual is symptomatic or not can be even more challenging than in a young patient. Dyspnea, for example, which is represented in a high proportion of symptomatic patients, may be due to a variety of causes ranging from a deconditioned athlete, to underlying lung or cardiac conditions. Similarly, atypical chest pain, palpitations, and dizziness have a relatively high prevalence in the general population but are mostly due to benign underlying causes (71). Myocardial perfusion defects attributed to the anomalous vessel in ACA is exceedingly rare in older patients and rather caused by CAD (59). Further, ACA seemed to demonstrate in this age group no increased risk of SCD at short-term follow-up (72). Why older individuals are less prone to ACA-related adverse cardiac events remains to be elucidated (73). Possible reasons include an age-related increase in aortic or coronary artery wall stiffness conferring less dynamic compression in older patients with ACA and a survivors' bias toward lower risk patients.

TO TREAT OR NOT TO TREAT: A DILEMMA. Several considerations must be considered before recommendations on exercise restriction or surgical therapy are offered to patients with ACA. First, exercise

FIGURE 2 Evaluation of "Asymptomatic" Individuals With Suspected or Incidental Finding of ACA



Treatment flow chart for evaluation of "asymptomatic" individuals with suspected or incidental finding of ACA. ACAOS = anomalous coronary arteries of the opposite sinus of Valsalva; IAC = interarterial course; other abbreviations as in Figure 1.

restriction would not necessarily prevent the possibility of SCD occurring at rest or with minimal activity. In addition, physicians should consider the psychological and emotional consequences of restricting exercise and the known health consequences of not exercising. Second, although post-operative outcome is favorable (29,70) and most reports of patients operated do not show abnormal stress tests post-operatively, a series from the Children's Hospital of Philadelphia reported that 38% surgical corrected patients had abnormal stress findings after correction (61). Furthermore, cases of SCD following successful surgical repair of ACA have been reported (74). This suggests that the benefits of surgery (or the value of the post-operative stress testing) are unclear (61). Third, to identify symptomatic patients due to an underlying ACA is challenging and ACA might be in most cases a coincidental finding. Furthermore, it has to be mentioned that 50% of SCDs associated with ACA were first events without prior symptoms (6,75), which adds to the challenges posed by this dilemma.

Fourth, pre-participation screening for ACA is difficult. The resting electrocardiogram in athletes with ACA is almost always normal. Furthermore, exercise treadmill testing remains negative in most patients with ACA, even in those who had symptoms suggestive of cardiac ischemia (6,40,76), and whether echocardiogram is a feasible and cost-effective screening tool in athletes is still in debate (76–79). Fifth, although ACA is one of the main underlying causes of SCD in athletes, one has to be aware that the absolute incidence remains very low, with 0.07 SCD per 100,000 person-athlete years (30). Similarly, in another large study, only 4 individuals died because of ACA in a combined 34 million patient-years (80).

Although there exists the dilemma of a very low absolute risk, it is widely accepted to surgically repair and restrict individuals from sports until corrected in left-ACAOS or any other form of ACA with symptoms or

signs of ischemia in athletes and nonathletes (29,70). If ischemic work-up is negative, then benefits from surgical recommendation and sports abstinence are questionable (81). Incorporating the current knowledge of the literature of ACA, we propose the following evaluation imaging steps, treatment options, and sport restriction recommendations. In symptomatic patients with either suspected or incidental finding of ACA, initial steps are coronary CTA for high-risk anatomic feature evaluation, followed by noninvasive ischemic testing. Depending on age and ischemic testing results, sports restriction with consecutive revascularization or further exclusion of CAD is recommended (**Figure 1**). In asymptomatic individuals with coincidental ACA, similar steps are recommended, and sports restriction and revascularization are based on age, high-risk anatomic features including discrimination between right-ACAOS and left-ACAOS, and ischemic testing (**Figure 2**). Because endpoints occur to few in athletes with ACA, prospective randomized controlled trials are not feasible in this patient group. Therefore, we strongly encourage the athletic and academic community to establish multicenter registries and to merge data from ongoing registries to further improve recommendations.

CONCLUSIONS

The diagnosis of ACA should not automatically mandate sports restriction and/or surgery. Any presumed prognostic benefits from surgical repair and sports restriction should be carefully balanced against possible impairments regarding quality of life in all age groups. Thus, decisions toward patient management should only be made after incorporating all clinical information, symptoms, age, sports behavior, and information of possible hemodynamical significance and high-risk features depicted by noninvasive imaging. Multimodality imaging plays a crucial role in the evaluation of individuals with ACA and guides patient management. However, more solid evidence based on large multicenter registries and follow-up studies is imperatively needed to modify current recommendations.

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REFERENCES

1. Angelini P, Flamm SD. Newer concepts for imaging anomalous aortic origin of the coronary arteries in adults. Catheter Cardiovasc Interv 2007;69:942–54.

2. Davis JA, Cecchin F, Jones TK, Portman MA. Major coronary artery anomalies in a pediatric population: incidence and clinical importance. J Am Coll Cardiol 2001;37:593–7.

3. Grani C, Benz DC, Schmied C, et al. Prevalence and characteristics of coronary artery anomalies detected by coronary computed tomography angiography in 5634 consecutive patients in a single centre in Switzerland. Swiss Med Wkly 2016;146:w14294.

4. Perez-Pomares JM, de la Pompa JL, Franco D, et al. Congenital coronary artery anomalies: a bridge from embryology to anatomy and pathophysiology. A position statement of the development, anatomy, and pathology ESC Working Group. Cardiovasc Res 2016;109:204–16.

5. Angelini P. Coronary artery anomalies: an entity in search of an identity. Circulation 2007;115:1296–305.

6. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. J Am Coll Cardiol 2000;35:1493–501.

7. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med 2004;141:829–34.

8. Kim SY, Seo JB, Do KH, et al. Coronary artery anomalies: classification and ECG-gated multidetector row CT findings with angiographic correlation. Radiographics 2006;26:317–33; discussion 333–4.

9. Lim JC, Beale A, Ramcharitar S. Anomalous origination of a coronary artery from the opposite sinus. Nat Rev Cardiol 2011;8:706–19.

10. Lorenz EC, Mookadam F, Mookadam M, Moustafa S, Zehr KJ. A systematic overview of anomalous coronary anatomy and an examination of the association with sudden cardiac death. Rev Cardiovasc Med 2006;7:205–13.

11. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and epidemiology of sudden deaths in young competitive athletes: from the United States National Registry. Am J Med 2016;129:1170–7.

12. Grani C, Chappex N, Fracasso T, et al. Sports-related sudden cardiac death in Switzerland classified by static and dynamic components of exercise. Eur J Prev Cardiol 2016;23:1228–36.

13. Pilmer CM, Kirsh JA, Hildebrandt D, Krahn AD, Gow RM. Sudden cardiac death in children and adolescents between 1 and 19 years of age. Heart Rhythm 2014;11:239–45.

14. Bogers AJ, Gittenberger-de Groot AC, Poelmann RE, Peault BM, Huysmans HA. Development of the origin of the coronary arteries, a matter of ingrowth or outgrowth? Anat Embryol (Berl) 1989;180:437–41.

15. 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.

16. Cheitlin MD, De Castro CM, McAllister HA. Sudden death as a complication of anomalous left coronary origin from the anterior sinus of Valsalva, a not-so-minor congenital anomaly. Circulation 1974;50:780–7.

17. Frescura C, Basso C, Thiene G, et al. Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease. Hum Pathol 1998;29:689–95.

18. Brothers JA, Whitehead KK, Keller MS, et al. Cardiac MRI and CT: differentiation of normal ostium and intraseptal course from slitlike ostium and interarterial course in anomalous left coronary artery in children. AJR Am J Roentgenol 2015;204:W104–9.

19. Sundaram B, Patel S, Bogot N, Kazerooni EA. Anatomy and terminology for the interpretation and reporting of cardiac MDCT. Part 1: structured report, coronary calcium screening, and coronary artery anatomy. AJR Am J Roentgenol 2009;192:574–83.

20. Cheezum MK, Ghoshhajra B, Bittencourt MS, et al. Anomalous origin of the coronary artery arising from the opposite sinus: prevalence and

outcomes in patients undergoing coronary CTA. Eur Heart J Cardiovasc Imaging 2017;18:224–35.

21. Harris MA, Whitehead KK, Shin DC, Keller MS, Weinberg PM, Fogel MA. Identifying abnormal ostial morphology in anomalous aortic origin of a coronary artery. Ann Thorac Surg 2015;100:174–9.

22. Miller JA, Anavekar NS, El Yaman MM, Burkhart HM, Miller AJ, Julsrud PR. Computed tomographic angiography identification of intramural segments in anomalous coronary arteries with interarterial course. Int J Cardiovasc Imaging 2012;28:1525–32.

23. Angelini P, Velasco JA, Ott D, Khoshnevis GR. Anomalous coronary artery arising from the opposite sinus: descriptive features and pathophysiologic mechanisms, as documented by intravascular ultrasonography. J Invasive Cardiol 2003;15:507–14.

24. Angelini P. Coronary artery anomalies–current clinical issues: definitions, classification, incidence, clinical relevance, and treatment guidelines. Tex Heart Inst J 2002;29:271–8.

25. Lawless CE. Return-to-play decisions in athletes with cardiac conditions. Phys Sportsmed 2009;37:80–91.

26. Penalver JM, Mosca RS, Weitz D, Phoon CK. Anomalous aortic origin of coronary arteries from the opposite sinus: a critical appraisal of risk. BMC Cardiovasc Disord 2012;12:83.

27. Thiene G, Carturan E, Corrado D, Basso C. Prevention of sudden cardiac death in the young and in athletes: dream or reality? Cardiovasc Pathol 2010;19:207–17.

28. Greenberg MA, Fish BG, Spindola-Franco H. Congenital anomalies of the coronary arteries. Classification and significance. Radiol Clin North Am 1989;27:1127–46.

29. Hill SF, Sheppard MN. A silent cause of sudden cardiac death especially in sport: congenital coronary artery anomalies. Br J Sports Med 2014;48:1151–6.

30. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation 2009;119:1085–92.

31. Ashrafpoor G, Danchin N, Houyel L, Ramadan R, Belli E, Paul JF. Anatomical criteria of malignancy by computed tomography angiography in patients with anomalous coronary arteries with an interarterial course. Eur Radiol 2015;25:760–6.

32. Jo Y, Uranaka Y, Iwaki H, Matsumoto J, Koura T, Negishi K. Sudden cardiac arrest: associated with anomalous origin of the right coronary artery from the left main coronary artery. Tex Heart Inst J 2011;38:539–43.

33. Fernandes F, Alam M, Smith S, Khaja F. The role of transesophageal echocardiography in identifying anomalous coronary arteries. Circulation 1993;88:2532–40.

34. Weiner RB, Wang F, Hutter AM Jr., et al. The feasibility, diagnostic yield, and learning curve of portable echocardiography for out-of-hospital cardiovascular disease screening. J Am Soc Echocardiogr 2012;25:568–75.

35. Zeppilli P, dello Russo A, Santini C, et al. In vivo detection of coronary artery anomalies in asymptomatic athletes by echocardiographic screening. Chest 1998;114:89–93.

36. Frommelt PC, Berger S, Pelech AN, Bergstrom S, Williamson JG. Prospective identification of anomalous origin of left coronary artery from the right sinus of valsalva using transthoracic echocardiography: importance of color Doppler flow mapping. Pediatr Cardiol 2001;22:327–32.

37. Turner II, Turek JW, Jaggers J, Herlong JR, Lawson DS, Lodge AJ. Anomalous aortic origin of a coronary artery: preoperative diagnosis and surgical planning. World J Pediatr Congenit Heart Surg 2011;2:340–5.

38. Lameijer H, Ter Maaten JM, Steggerda RC. Additive value of dobutamine stress echocardiography in patients with an anomalous origin of a coronary artery. Neth Heart J 2015;23:139–40.

39. Osaki M, McCrindle BW, Van Arsdell G, Dipchand AI. Anomalous origin of a coronary artery from the opposite sinus of Valsalva with an interarterial course: clinical profile and approach to management in the pediatric population. Pediatr Cardiol 2008;29:24–30.

40. Frommelt PC, Frommelt MA, Tweddell JS, Jaquiss RD. Prospective echocardiographic diagnosis and surgical repair of anomalous origin of a coronary artery from the opposite sinus with an interarterial course. J Am Coll Cardiol 2003;42:148–54.

41. Zeltser I, Cannon B, Silvana L, et al. Lessons learned from preparticipation cardiovascular screening in a state funded program. Am J Cardiol 2012;110:902–8.

42. Lorber R, Srivastava S, Wilder TJ, et al. Anomalous aortic origin of coronary arteries in the young: echocardiographic evaluation with surgical correlation. J Am Coll Cardiol Img 2015;8:1239–49.

43. Ghadri JR, Kazakauskaite E, Braunschweig S, et al. Congenital coronary anomalies detected by coronary computed tomography compared to invasive coronary angiography. BMC Cardiovasc Disord 2014;14:81.

44. Fuchs TA, Stehli J, Bull S, et al. Coronary computed tomography angiography with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination. Eur Heart J 2014;35:1131–6.

45. Benz DC, Grani C, Hirt Moch B, et al. Minimized radiation and contrast agent exposure for coronary computed tomography angiography: first clinical experience on a latest generation 256-slice scanner. Acad Radiol 2016;23:1008–14.

46. Bunce NH, Lorenz CH, Keegan J, et al. Coronary artery anomalies: assessment with free-breathing three-dimensional coronary MR angiography. Radiology 2003;227:201–8.

47. Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2614–62.

48. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J 2010;31:794–805.

49. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): consensus panel report. J Cardiovasc Magn Reson 2004;6:727–65.

50. Ripley DP, Saha A, Teis A, et al. The distribution and prognosis of anomalous coronary arteries identified by cardiovascular magnetic resonance: 15 year experience from two tertiary centres. J Cardiovasc Magn Reson 2014;16:34.

51. Taylor AM, Thorne SA, Rubens MB, et al. Coronary artery imaging in grown up congenital heart disease: complementary role of magnetic resonance and x-ray coronary angiography. Circulation 2000;101:1670–8.

52. Brothers JA, Kim TS, Fogel MA, et al. Cardiac magnetic resonance imaging characterizes stenosis, perfusion, and fibrosis preoperatively and postoperatively in children with anomalous coronary arteries. J Thorac Cardiovasc Surg 2016;152:205–10.

53. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. Circulation 2008;118:586–606.

54. Prakken NH, Cramer MJ, Olimulder MA, Agostoni P, Mali WP, Velthuis BK. Screening for proximal coronary artery anomalies with 3-dimensional MR coronary angiography. Int J Cardiovasc Imaging 2010;26:701–10.

55. Zeina AR, Blinder J, Sharif D, Rosenschein U, Barmeir E. Congenital coronary artery anomalies in adults: non-invasive assessment with multidetector CT. Br J Radiol 2009;82:254–61.

56. Mavrogeni S, Spargias K, Karagiannis S, et al. Anomalous origin of right coronary artery: magnetic resonance angiography and viability study. Int J Cardiol 2006;109:195–200.

57. De Luca L, Bovenzi F, Rubini D, Niccoli-Asabella A, Rubini G, De Luca I. Stress-rest myocardial perfusion SPECT for functional assessment of coronary arteries with anomalous origin or course. J Nucl Med 2004;45:532–6.

58. Uebleis C, Groebner M, von Ziegler F, et al. Combined anatomical and functional imaging using coronary CT angiography and myocardial perfusion SPECT in symptomatic adults with abnormal origin of a coronary artery. Int J Cardiovasc Imaging 2012;28:1763–74.

59. Grani C, Benz DC, Schmied C, et al. Hybrid CCTA/SPECT myocardial perfusion imaging findings in patients with anomalous origin of coronary arteries from the opposite sinus and suspected concomitant coronary artery disease. J Nucl Cardiol 2017;24:226–34.

60. Grani C, Benz DC, Possner M, et al. Fused cardiac hybrid imaging with coronary computed tomography angiography and positron emission tomography in patients with complex coronary artery anomalies. Congenit Heart Dis 2017;12:49–57.

61. Brothers JA, McBride MG, Seliem MA, et al. Evaluation of myocardial ischemia after surgical repair of anomalous aortic origin of a coronary artery in a series of pediatric patients. J Am Coll Cardiol 2007;50:2078–82.

62. Lim MJ, Forsberg MJ, Lee R, Kern MJ. Hemodynamic abnormalities across an anomalous left main coronary artery assessment: evidence for a dynamic ostial obstruction. Catheter Cardiovasc Interv 2004;63:294–8.

63. Nasis A, Machado C, Cameron JD, Troupis JM, Meredith IT, Seneviratne SK. Anatomic characteristics and outcome of adults with coronary arteries arising from an anomalous location detected with coronary computed tomography angiography. Int J Cardiovasc Imaging 2015;31:181–91.

64. Pelliccia A, Fagard R, Bjornstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2005;26:1422–45.

65. Graham TP Jr., Driscoll DJ, Gersony WM, Newburger JW, Rocchini A, Towbin JA. Task Force 2: congenital heart disease. J Am Coll Cardiol 2005;45:1326–33.

66. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: a consensus document. Eur J Cardiovasc Prev Rehabil 2006;13:293–9.

67. Gersony WM. Management of anomalous coronary artery from the contralateral coronary sinus. J Am Coll Cardiol 2007;50:2083–4.

68. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e143–263.

69. Van Hare GF, Ackerman MJ, Evangelista JA, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 4: congenital heart disease: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol 2015;66:2372–84.

70. Krasuski RA, Magyar D, Hart S, et al. Long-term outcome and impact of surgery on adults with coronary arteries originating from the opposite coronary cusp. Circulation 2011;123:154–62.

71. Grani C, Senn O, Bischof M, et al. Diagnostic performance of reproducible chest wall tenderness to rule out acute coronary syndrome in acute chest pain: a prospective diagnostic study. BMJ Open 2015;5:e007442.

72. Opolski MP, Pregowski J, Kruk M, et al. Prevalence and characteristics of coronary anomalies originating from the opposite sinus of Valsalva in 8,522 patients referred for coronary computed tomography angiography. Am J Cardiol 2013;111:1361–7.

73. Taylor AJ, Byers JP, Cheitlin MD, Virmani R. Anomalous right or left coronary artery from the contralateral coronary sinus: "high-risk" abnormalities in the initial coronary artery course and heterogeneous clinical outcomes. Am Heart J 1997;133:428–35.

74. Nguyen AL, Haas F, Evens J, Breur JM. Sudden cardiac death after repair of anomalous origin of left coronary artery from right sinus of Valsalva with an interarterial course: case report and review of the literature. Neth Heart J 2012;20:463–71.

75. Frommelt PC. Congenital coronary artery abnormalities predisposing to sudden cardiac death. Pacing Clin Electrophysiol 2009;32 Suppl 2:S63–6.

76. Corrado D, Pelliccia A, Bjornstad HH, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2005;26:516–24.

77. Drezner JA, Ackerman MJ, Anderson J, et al. Electrocardiographic interpretation in athletes: the "Seattle criteria." Br J Sports Med 2013;47:122–4.

78. Pelliccia A, Spataro A, Maron BJ. Prospective echocardiographic screening for coronary artery anomalies in 1,360 elite competitive athletes. Am J Cardiol 1993;72:978–9.

79. Wyman RA, Chiu RY, Rahko PS. The 5-minute screening echocardiogram for athletes. J Am Soc Echocardiogr 2008;21:786–8.

80. Meyer L, Stubbs B, Fahrenbruch C, et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. Circulation 2012;126:1363–72.

81. Brothers JA, Paridon SM. The new AHA/ACC guidelines for competitive sports participation in young athletes with anomalous coronary arteries: the evolution of change. World J Pediatr Congenit Heart Surg 2016;7:241–4.

KEY WORDS ACA, ACAOS, anomalous coronary arteries, athletes, CMR, competitive sports, coronary CTA, multimodality imaging, sudden cardiac death