REVIEW

Anomalous coronary arteries: what is known and what still remains to be learned?

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Purpose of review
To report what is known and unknown regarding coronary anomalies in children, particularly anomalous aortic origin of a coronary artery, efforts undertaken to answer several questions regarding evaluation and management of this challenging young population, and where the future is heading.

Recent findings
Patients with anomalous aortic origin of a coronary artery (AAOCA) present as an incidental finding at least half of the time, advanced imaging is essential to define anatomic characteristics of this lesion, assessment of myocardial perfusion with stress cardiac magnetic resonance imaging is feasible and contributes to risk stratification, certain patient populations require invasive assessment of coronary flow with measurement of fractional flow reserve, and surgical intervention can be safely performed through long-term data on impact to prevent sudden events is lacking.

Summary
Optimal risk stratification in AAOCA is yet to be defined, though substantial strides are being made with a standardized approach to the evaluation and management of these patients. Continued collaboration among centers and the scientific community will positively impact patients and families living with AAOCA.

Keywords
anomalous coronary arteries, coronary anomalies, myocardial ischemia, sudden death

INTRODUCTION TO CORONARY ANOMALIES

Coronary artery anomalies are an assorted group of congenital heart disease with variable pathophysiology, clinical presentation, and implications. Of all the types, anomalous aortic origin of a coronary artery (AAOCA) is identified as the one with the highest risk of sudden cardiac death (SCD) in young athletes [1,2]. This review focuses on AAOCA, where the origin of a coronary artery arises from the opposite sinus of Valsalva, thereby having an interarterial course between the great arteries (Fig. 1), detailing its clinical presentation, clinical significance, diagnosis, and approach to management.

This anomaly can involve either the right coronary arising from the left sinus of Valsalva (AAORCA, reportedly more common) or the left coronary arising from the right sinus of Valsalva (AAOLCA) and rarely having a near commissural origin posteriorly. The true prevalence of AAOCA in the general population remains unknown studies have focused primarily on symptomatic patients. The estimated frequency of AAOLCA is 0.03–0.15%, whereas that of AAORCA is 0.28–0.92% [3,4].

AAOCA is known to be the 2nd leading cause of SCD in young athletes estimated to be responsible for 15–20% of sudden death in this population [1,2]. The risk of SCD appears highest in young individuals, particularly during or following a period of strenuous exertion, and particularly in those with interarterial AAOLCA. Studies of adult cohorts with AAORCA undergoing conservative therapy have observed a very low mortality (<1%) in about 1–5 years of follow-up [4,5].

RELEVANCE, CLINICAL PRESENTATION, AND DIAGNOSIS

In recent studies about 50% of patients have been noted to be asymptomatic at diagnosis

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KEY POINTS

- Advanced imaging is essential to define anatomic characteristics of anomalous aortic origin of a coronary artery.
- Assessment of myocardial perfusion is critical for risk stratification of this population and stress cardiac magnetic resonance imaging has shown to be of substantial value.
- Patients with anomalous aortic origin of a coronary artery and long intramyocardial course with evidence of ischemia on advanced imaging require invasive assessment of coronary flow with measurement of fractional flow reserve.
- Optimal risk stratification in AAOCA is yet to be defined, though substantial strides are being made with a standardized approach to the evaluation and management of these patients.
- Continued collaboration among centers and the scientific community will positively impact patients and families living with AAOCA.

[2,6▪,7,8▪▪,9,10]. An increasing number of children and adolescents are being diagnosed with AAOCA following routine preparticipation screening, presence of a murmur, or an abnormal ECG [8▪▪,9]. Typically presenting symptoms that have been reported are exertional chest pain, palpitations, syncope, as well as sudden cardiac arrest (SCA) [9,10].

Several pathophysiologic mechanisms have been postulated for the occurrence of SCA/SCD in patients with AAOCA. These include occlusion and/or compression of the anomalous coronary artery (intramural segment, interarterial course) and ostial abnormalities (slit-like and stenotic ostium), particularly during exercise, leading to myocardial ischemia and development of ventricular arrhythmia [6▪]. In a study by Basso *et al.* [1] among others, of 27 individuals who experienced SCD because of AAOCA, only 10 presented with symptoms prior to the event. Given the significant number of patients that are asymptomatic prior to a critical adverse cardiac event, this highlights difficulties in evaluating patients at risk for adverse sudden cardiac events.

Transthoracic echocardiography (TTE) is the first-line imaging modality for initial diagnosis [11,12]. Recent report by Lorber *et al.* [12] found variable agreement between the TTE and surgical findings. In another study, TTE reliably and prospectively diagnosed AAOCA in more than 95% of the cohort, and the echo findings were always consistent with the surgical descriptions of the anatomy [8▪▪]. Lorber *et al.* suggested that apart from the uses of TTE in the diagnosis of the abnormal coronary origins, TTE can also be helpful in identifying critical anatomical features like intramural/interarterial course that may influence surgical management. However, they demonstrated that assessment of coronary ostium as well as intramyocardial course was not well delineated by TTE. Thus, advanced imaging modalities, including computed tomography angiography (CTA) or cardiac magnetic resonance imaging (CMR) are extremely helpful in comprehensively defining the anatomy of the AAOCA, including ostial morphology, interarterial, intramural, or intramyocardial course [13–20].

Retrospectively ECG-gated coronary CTA provides accurate assessment of the coronary anatomy including site of egress of the coronary artery with respect to the opposite coronary artery/sinus, aortic valve commissures and level of origin [9,14,21▪▪]. Virtual angioscopy/fly through technique gives details of ostial morphology and can help identifying ostial stenosis. CTA also helps to analyze precisely the intramural length of the anomalous coronary artery given change in caliber of the coronary artery from its intramural to extramural course. (Fig. 2) [6▪] Moreover, because of short-scan time, CTA does not require sedation in younger children, and the amount of ionizing radiation has significantly decreased with new-generation scanners. Given these advantages, all patients diagnosed with or suspected to have AAOCA on TTE undergo a coronary CTA at our institution [9,22,23▪▪].

CMR provides valuable functional assessment that complements the anatomic information derived from CTA. This includes assessment of ventricular function, myocardial perfusion abnormalities (Fig. 3) as well as wall motion abnormalities at rest and with pharmacological stress and myocardial viability [16,18,22,24]. Some institutions utilize CMR to even delineate coronary anatomy via reparatory-gated navigator sequences [17]. Advantages of CMR assessment include lack of exposure to ionizing radiation although younger children almost always need sedation. At our institution every patient diagnosed with AAOCA undergoes a stress cardiac magnetic resonance (sCMR) for appropriate risk stratification and evaluate indication for surgery, if perfusion defects are identified [22]. Previously, stress nuclear perfusion imaging (sNPI) was utilized to evaluate myocardial perfusion. However, given high-false positive and false-negative rates, this modality has been largely replaced by stress CMR [20,25]. Stress CMR with dobutamine has been shown to be feasible, safe, and well tolerated in the pediatric population [16,25,26].

Exercise stress test (EST) is a traditional provocative test used to evaluate patients with AAOCA for

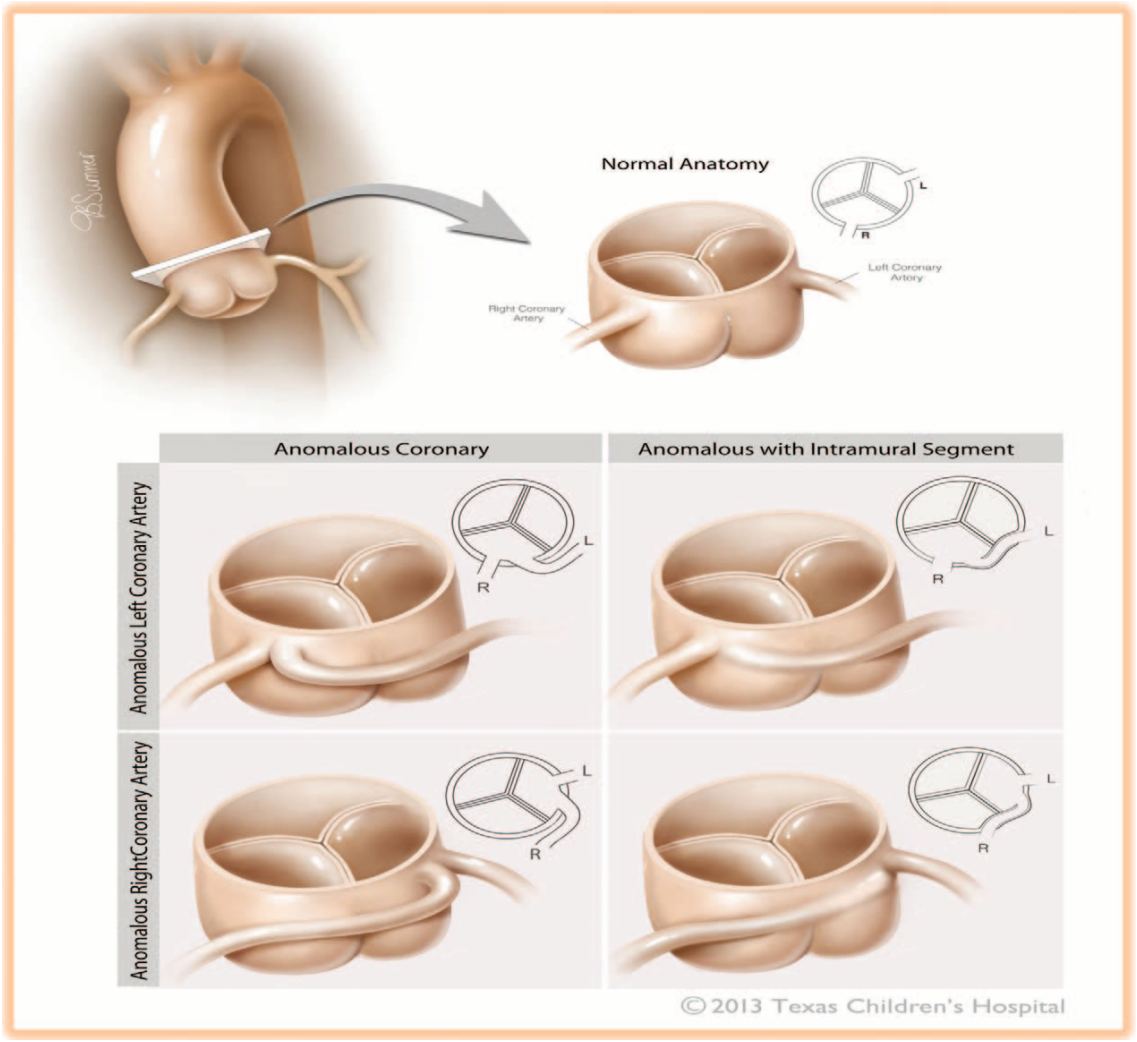

FIGURE 1. Diagram illustrating normal coronary artery origins and anomalous aortic origin of a coronary artery from the opposite sinus of Valsalva with and without intramural course. Printed with permission from Texas Children's Hospital © 2013. Adapted from Molossi *et al.* [48].

any evidence of ischemia, given with stress test changes or ventricular arrhythmias. However, there are mixed data regarding its validity with only 5–8% of patients who undergo surgery are noted to have an abnormal EST [8▪▪,9,20,21▪▪,22]. In our program, 8% of patients have an abnormal EST [9].

Cardiac catheterization has been utilized in conjunction with intravascular ultrasound to assess degree of coronary stenosis in the intramural segment, as demonstrated by Angelini *et al.*[27,28]. Cardiac catheterization has also been utilized in certain patients, especially with an intramyocardial segment to assess fractional flow reserve (FFR) with pharmacological stress. We have used cardiac catheterization with FFR measurement with dobutamine for risk stratification in this selected group of patients, and it has allowed us to identify a significant decrease in the flow of coronary arteries with an intramyocardial segment [29].

STANDARDIZED APPROACH TO EVALUATION AND MANAGEMENT

Establishing a multidisciplinary team

As we have previously shown, there is a wide variety of approaches to the diagnosis and management of patients with coronary anomalies [30]. Challenging questions are posed by patients and families to which there are no answers based on prospective, longitudinal data. Given so many uncertainties, including optimal risk stratification, identification

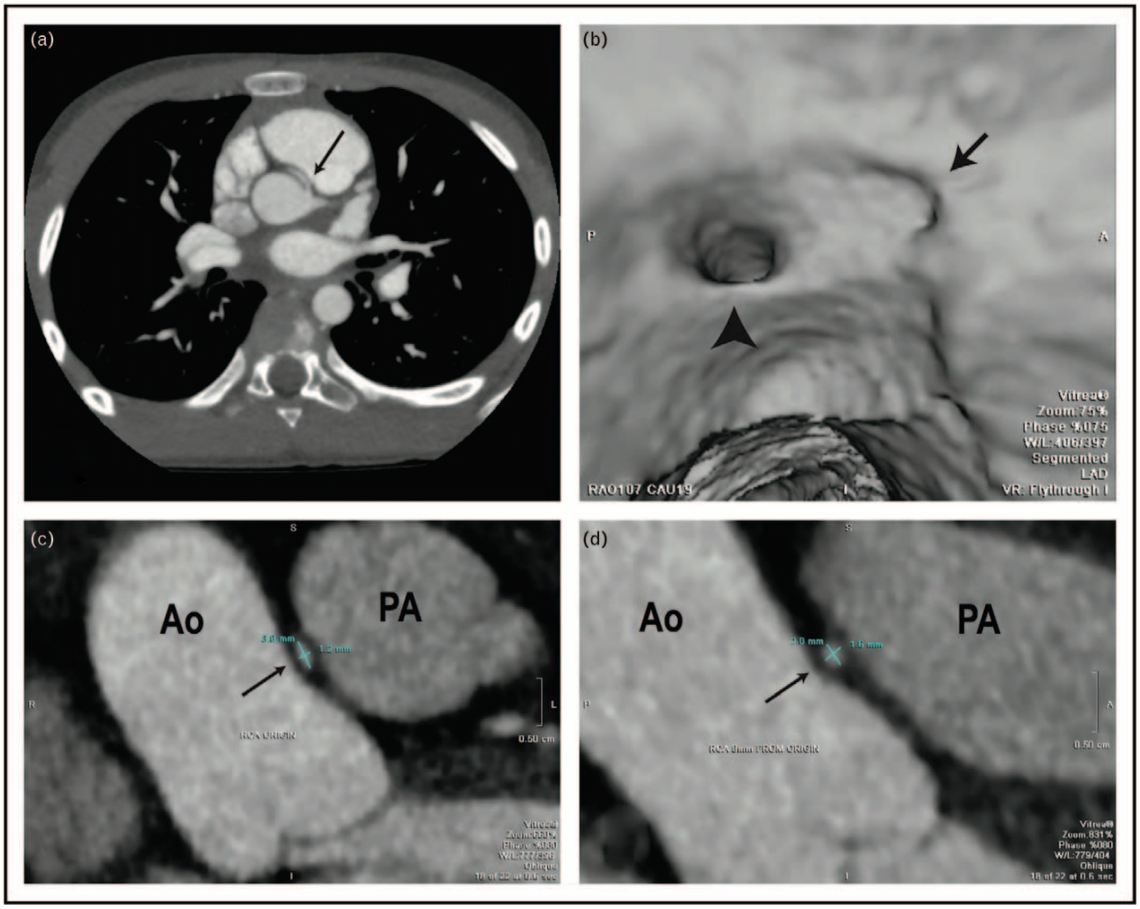

FIGURE 2. Computerized tomographic angiography demonstrating an anomalous right coronary artery. (a) The anomalous right coronary arises from the left sinus with an intramural course as it courses in between the aorta and the pulmonary artery. (b) Virtual angioscopy shows a normal left coronary ostium (arrowhead) and the anomalous right coronary with a stenotic slit-like ostium arising just above and to the left of the intercoronary commissure. (c) The anomalous coronary (arrow) has an oval shape on its intramural segment compared with (d) the round shape of the distal coronary past its intramural segment. Printed with permission from Texas Children's Hospital © 2014. Adapted from Molossi *et al.* [6▪]. *Ao*, Aorta; *PA*, pulmonary artery.

of myocardial ischemia, risk of sudden cardiac events, and impact of surgical intervention on outcomes, the scientific community has come together to obtain much-needed data. We developed, at Texas Children's Hospital, the first dedicated Coronary Anomalies Program (CAP) in December 2012. This consists of a multidisciplinary team of pediatric and adult cardiologists, surgeons, cardiovascular radiologists, cardiovascular anesthesiologists, nurses, and research and outcome staff. A standardized approach to the evaluation and management of these patients was proposed, based on available data and team discussion, and followed with every patient evaluated in the program. The CAP team holds meetings every 2 weeks to discuss all patients seen. This has allowed continuous learning based on data acquired through quality-assurance meetings held every 1–2 years [22]. The latest iteration of the clinical algorithm followed in the CAP, from January 2018, is depicted in Fig. 4. Several efforts are occurring nationally to obtain meaningful data that will greatly contribute to the care of patients with AAOCA [31].

Advanced imaging

Most patients are diagnosed with AAOCA by TTE, study performed in at least half of patients because of an incidental finding upon being evaluated for an innocent murmur or abnormal ECG. However, despite some centers excelling in determining the type and course of coronary anomaly [12], details of the anatomy will be defined with advanced imaging, such as CTA or CMR imaging. Given the difficulty in precisely determining the length of

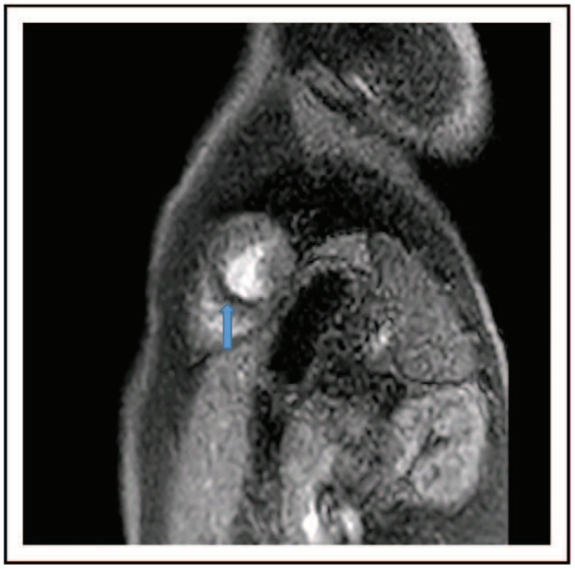

FIGURE 3. Cardiac magnetic resonance imaging with dobutamine stress demonstrating a subendocardial perfusion defect in the inferior septum (blue arrow) in a patient with anomalous right coronary from the left sinus of Valsalva. Printed with permission from Texas Children's Hospital not published © 2019.

intramural course with CMR, we have adopted the routine use of retrospectively ECG-gated CTA. The presence and length of intramural course are determined using cross-sectional shape of the lumen and the pericoronary fat sign, a tool described by our institution [32]. A topography map was created in our program to better define ostial location in relation to the specific coronary sinus and commissures (Fig. 5). The type of AAOCA, ostial morphology and location (Fig. 6), and presence and length of intramural and or intraseptal course is described in a standardized report. We have observed that most anomalous coronaries appear to arise from the opposite sinus just beyond the commissure between the anterior sinuses and with a high take-off (levels III–IV).

Myocardial functional assessment

All patients evaluated in our program undergo myocardial functional studies to determine the presence of myocardial ischemia, except those of young age with no concerning symptoms ascribed to ischemia or those presenting with SCA. A cardiopulmonary EST is performed using the standard Bruce protocol. In our experience, ischemic changes are rarely observed [33]. Previous reports have described low sensitivity of exercise stress test to identify ischemia and inconsistency in findings [34].

Assessment of myocardial perfusion has become an integral part of the evaluation of patients with AAOCA for risk stratification. Some centers utilize stress echocardiography to identify wall motion abnormalities. We utilized sNPI at the beginning of our program. However, the incidence of false-positive and false-negative findings [35], decreased spatial resolution and attenuation artifacts related to the body wall and diaphragm movement, and the use of ionizing radiation led to discouragement in continuing its use. sCMR has become our preferred mode of evaluating perfusion abnormalities in our patient population, in addition to provide information on wall motion and myocardial viability. It provides high-quality cardiac imaging with excellent spatial resolution, it is feasible and well tolerated in children [25], does not utilize ionizing radiation, and demonstrated better sensitivity and specificity when compared with sNPI [35]. Given the dynamic nature of the presumed mechanism leading to impairment of flow in AAOCA, dobutamine is preferred as a provocative agent to induce stress, increasing cardiac inotropy and chronotropy and simulating physiologic exercise condition [29,36]. Atropine may also be used to achieve the desired increase to 85% predicted peak heart rate.

Invasive assessment of coronary flow

Invasive assessment of coronary flow is performed with measurement of FFR during cardiac catheterization, a reference standard given its inability to be affected by heart rate, myocardial contractility and blood pressure [37,38]. In some types of coronary anomalies, measurement of FFR has been particularly useful in risk stratification. In our program, patients underwent cardiac catheterization with FFR measurement in the presence of an intramyocardial segment with specific clinical concerns such as symptoms ascribed to ischemia or myocardial perfusion abnormalities on stress imaging. Selective coronary angiography with FFR assessment upon administration of adenosine and/or dobutamine (with similar target heart rate as with sCMR) is performed. In some cases, intravascular ultrasound is also performed to estimate the degree of obstruction during the cardiac cycle. We have previously reported our experience demonstrating feasibility and safety in children [29].

Clinical decision-making

The counseling of patients and families with AAOCA is quite defying given the many unknowns surrounding these anomalies. The exact risk of sudden death is unknown and the circumstances leading to the sudden event is often associated with

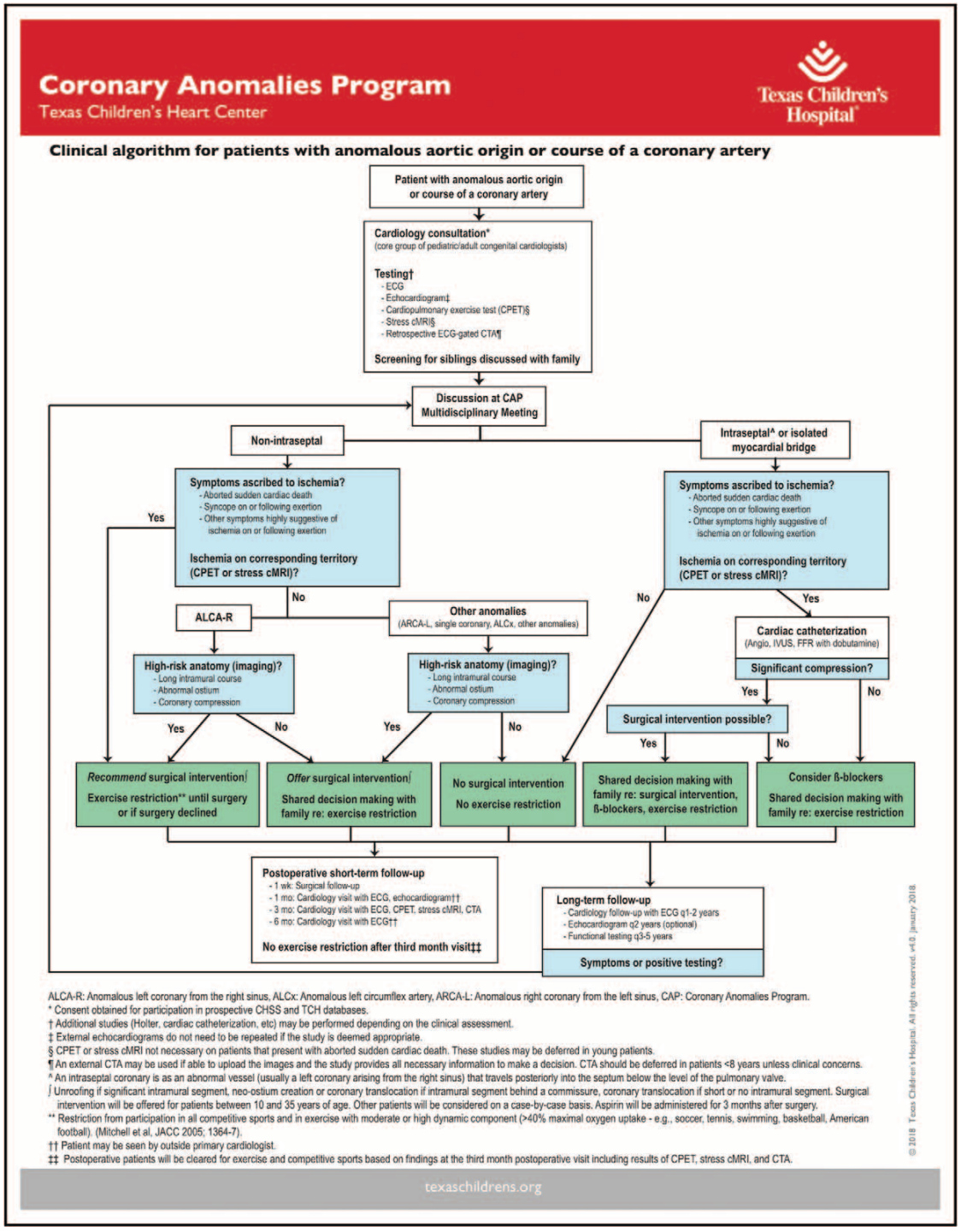

FIGURE 4. Algorithm for the evaluation and management of patients with coronary anomalies in the Coronary Anomalies Program at Texas Children's Hospital. Printed with permission from Texas Children's Hospital © 2018. Adapted from Mery *et al.* [23▪▪].

exertion, but not solely. Furthermore, it remains unknown why an athlete can participate vigorously in sports/exercise activities for many years until the sentinel event occurs. Indeed, approximately half of patients are diagnosed with AAOCA incidentally, but the other half may present with symptoms. In fact, patients presenting with SCD or SCA have reported symptoms prior to the event [1].

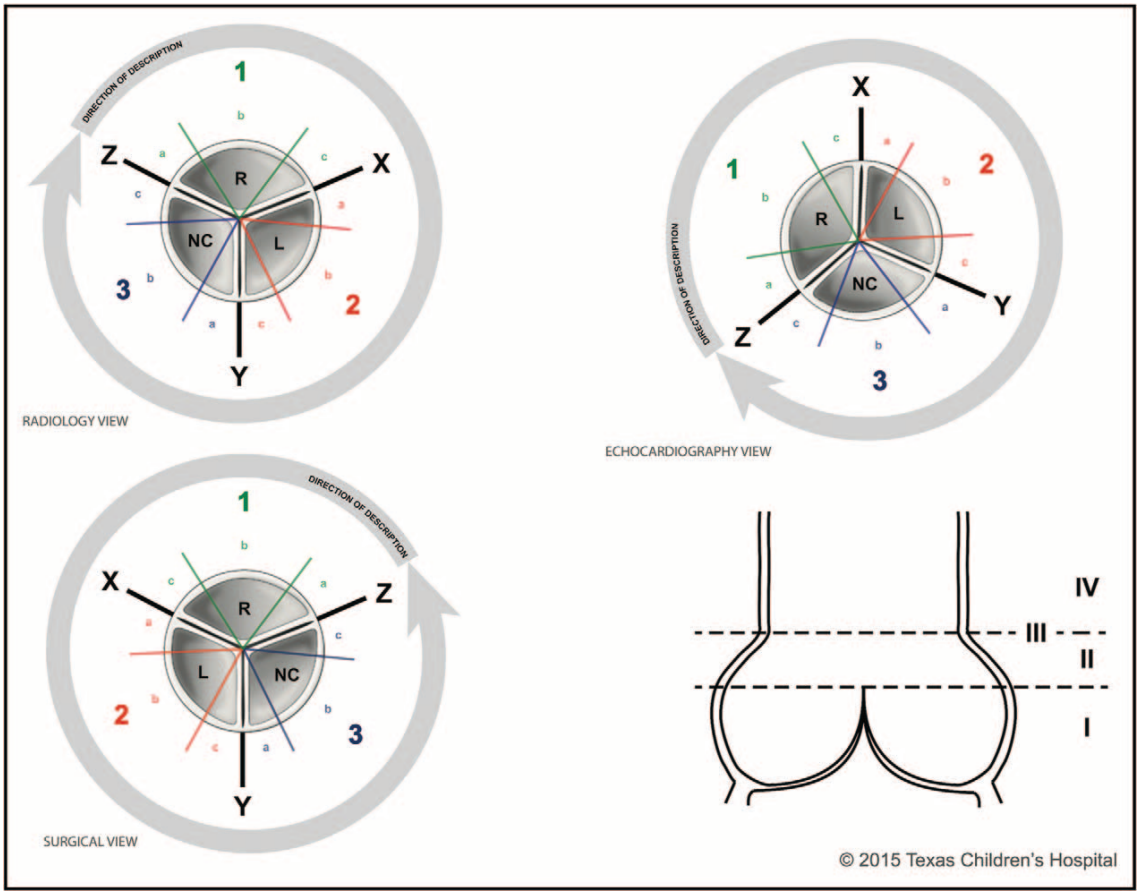

FIGURE 5. Topography map developed at the Coronary Anomalies Program for precise determination of ostium location. Printed with permission from Texas Children's Hospital © 2015. Adapted from Molossi *et al.* [48]. *L*, left coronary sinus; *R*, right coronary sinus; *NC*, noncoronary sinus.

Management of patients with these coronary anomalies is even more challenging as there is lack of long-term data on outcomes of both repaired and unrepaired populations. The current American Heart Association/American College of Cardiology statement [39] and American Association for Thoracic Surgery guidelines [40] have differentiated the considered high-risk interarterial AAOLCA and the considered low-risk interarterial AAORCA. However, recommendations suggest no need for intervention in asymptomatic patients with AAORCA in the presence of a normal EST. Basso *et al.* [1] have reported patients with normal EST prior to suffering SCD. In our CAP, we also have seen patients with normal EST, no concerning symptoms, and evidence of perfusion abnormalities on advanced imaging with sCMR. In addition, we have seen patients with high origin of the coronary artery with lengthy intramural course and anomalous coronaries with intraseptal course and evidence of ischemia [41▪▪] without translation on ischemic changes on EST. Risk stratification remains the Holy Grail, the scientific community is in pursuit [42]. In developing a standardized approach in the CAP, we have attempted to risk stratify patients arbitrarily according to low and high-risk categories, at the same time that we acquired prospective data to reevaluate our strategy/algorithm.

Management – clinical versus surgical

Discussion with the patient and family is undertaken upon completing the evaluation and the data reviewed at the multidisciplinary team meeting of the CAP. Management strategy follows our algorithm depicted in Fig. 4. Patients with AAOLCA and high-risk anatomy (origin from the opposite sinus with interarterial and/or intramural course, commissural origin with ostial abnormalities, and intramural course in the setting of inducible myocardial ischemia) are offered surgical intervention. Patients with other coronary anomalies, most

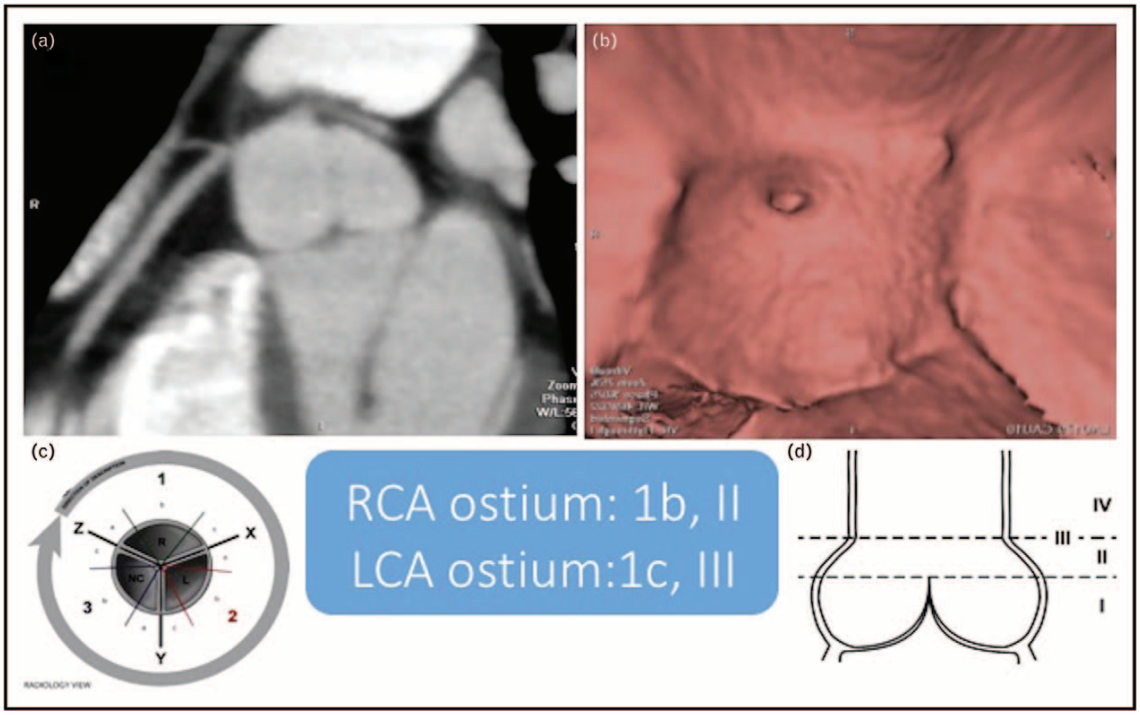

FIGURE 6. Computerized tomography angiography depicting an anomalous aortic origin of the left coronary artery from the right sinus of Valsalva (a) and virtual angioscopy depicting ostial morphology (b) with corresponding location based on topography map (c and d). Printed with permission from Texas Children's Hospital © 2013, not published.

commonly AAORCA from the opposite sinus, are offered surgical intervention if they have concerning characteristics such as symptoms clearly ascribed to ischemia, a positive myocardial functional study, or what the team believes to be high-risk anatomy such as a long intramural course and ostial abnormalities in the setting of persistent symptoms and upon shared decision-making with the family. Early in our program, we offered surgical intervention in asymptomatic patients with AAORCA from the opposite sinus with long intramural course (above 5 mm) [33] regardless of symptomatology. However, we have veered away from this practice largely because of the development of our sCMR program in the last few years that provides high accuracy on myocardial perfusion and wall motion assessment, in addition to more experience acquired on following patients with longer intramural course and remaining asymptomatic. Patients with anatomy deemed unsuitable to surgical intervention, because of long intramyocardial course, who have ischemic symptoms or positive myocardial functional studies are recommended exercise restriction and prescribed β-blocker therapy, again following extensive discussion with the family and shared decision-making. We have observed that a small group of patients with AAOCA and intraseptal course, at times extending beyond the conal septum and extending further down into the ventricular septum with a longer intramyocardial course, have clear evidence of ischemia. Surgical strategies are very complex with unclear benefit in relieving the obstruction within the long segment, thus exercise restriction is discussed and recommended, plus/minus β-blocker therapy.

Surgical techniques utilized in the repair of AAOCA include, most frequently, the unroofing procedure [43], coronary translocation with reimplantation in the correct sinus [44], neoostium creation [45], pulmonary translocation [46,47]. Our surgical experience in 44 patients has been previously published (80% AAORCA, 20% AAOLCA) [23▪▪]. Approximately 25% of patients with AAORCA in our cohort were recommended to undergo surgical intervention. The surgical procedure has proven quite well tolerated in experienced hands, though some complications are encountered, most frequently postcardiotomy syndrome in our cohort (9%) [23▪▪]. It remains to be established of surgical intervention alters the natural history of these patients and positively impacts in minimizing/eliminating the risk for SCD/SCA.

All patients are followed at particular time intervals (Fig. 4), regardless of undergoing an intervention. Those patients undergoing surgery are reevaluated at 1 month postoperatively with ECG

and echocardiogram and at 3 months postoperatively with ECG, myocardial functional studies, and CTA (same studies performed on initial presentation). Patients are allowed to return to full exercise activities and competitive sports participation, following reconditioning period, if studies performed at this time are reassuring. Largely, exercise restriction is only recommended for patients awaiting surgical intervention, during the 3 months postoperatively, high-risk lesions refusing surgical intervention, or those deemed unsuitable to the current surgical strategies given long intraseptal/intramyocardial course. Patients deemed to have low-risk lesions are not offered surgical intervention and are allowed unrestricted exercise activities.

WHERE WILL THE FUTURE TAKE US?

A diagnosis of AAOCA is a life-changing experience to patients and families and challenges care providers. Unquestionably, large strides are being taken toward better definition of risk stratification, identification of myocardial ischemia, and evaluation of outcomes in both natural and unnatural (repaired) AAOCA. It is paramount that models be developed to study the mechanisms whereby the coronary flow is affected and relate to the type of coronary anomaly, ostial morphology, intramural and interarterial course, and optimally how it changes with exercise. With the advance of noninvasive imaging, measurement of FFR by CTA and determination of wall shear stress will hopefully provide some answers. Collaboration among centers caring for these patients and gather of prospective data is essential, as is the development of resources to support patients and families living with AAOCA.

CONCLUSION

A standardized approach to the evaluation and management of patients with AAOCA has provided prospective and longitudinal data to better understand the natural and unnatural history of this condition. However, optimal risk stratification is still lacking and current efforts to unravel mechanisms of coronary blood flow and how the anatomic features impact myocardial perfusion are ongoing. Lastly, it is of utmost importance that resources are developed to offer support to patients and families living with AAOCA, a condition impacting quality of life.

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Conflicts of interest

There are no conflicts of interest.

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