Review Article

Coronary artery anomalies: what are they? when to suspect? how to treat?—a narrative review

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Background and Objective: In the literature have been widely discussed different classification criteria for coronary artery anomalies (CAAs), some authors have tried to categorize them only as "major" or "hemodynamically significant" anomalies versus "minor" or "not hemodynamically significant" ones. However, the most recent literature has concluded that all possible coronary anatomy should be taken into consideration in a comprehensive classification of CAAs. The aim of the article is to review the most recent literature regarding CAAs to provide a comprehensive overview of this challenging topic.

Methods: We propose a narrative overview of the most impactful and recent literature, synthetizing and re-elaborating the most important articles concerning CAAs.

Key Content and Findings: The important gap of knowledge on the specific characteristics of CAAs has led to a progressively increased interest of the current research in this field. Albeit their nature is still unclear, an increased awareness of their fatality is spreading among clinicians and the general population, mostly associated with their clinical relevance among young patients and athletes. On the other side, we do believe that clinical and hemodynamic repercussions are of crucial importance and should always be integrated to understand the true nature of this important pathology.

Conclusions: In the field of pediatric cardiology, CAAs are one of the most fascinating and studied subject. We propose a state-of-the art review to provide a comprehensive and systematic description and subsequently an approach to the epidemiological, pathophysiological, and clinical aspects of the most important CAAs in the pediatric population.

Keywords: Anomalous coronary artery; coronary anomaly; sudden cardiac death (SCD); congenital heart disease; myocardial dysfunction

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Introduction

Coronary artery anomalies (CAAs) represent one of the most controversial topics in the cardiology field, leaving the pediatric cardiologist with even less certitude. An increased awareness of their fatality is spreading, even if the reasons for the sudden fatal event and the frequency with which it occurs remains still unclear. In the literature have been widely discussed different classification criteria for CAAs, some authors have tried to categorize them only as "major" or "hemodynamically significant" anomalies versus "minor" or "not hemodynamically significant" ones. However, the most recent literature has concluded that all possible coronary anatomy should be taken into consideration in a comprehensive classification of CAAs, independently from the hemodynamic and clinical repercussion of each (1).

CAAs may be classified into those of origin and course, intrinsic coronary arterial anatomy, of coronary termination and anomalous anastomotic vessels (2). The most common malformation is abnormal origin and course, either from the wrong aortic coronary sinus either from the pulmonary artery (PA). The aim of this article is to review current literature to promote a systematical approach to the epidemiological, pathophysiological and clinical aspects of the most important CAAs in pediatric population. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-30/rc).

Methods

We thoroughly searched on PubMed database for all the publications concerning CAAs from 1960 to 2023, collecting the most relevant articles including neonatal, pediatric, and adult patients diagnosed with and treated for CAAs. Case series, registries and reviews have been included in the present research. The search strategy summary and a detailed search strategy for PubMed database are shown in *Table 1* and Table S1, respectively. Therefore, we propose a narrative overview of the most impactful and recent literature, synthetizing and re-elaborating the most important articles concerning CAAs.

CAAs: classification

Table 2 shows a schematic classification of the main CAAs.

CAAs can be classified as:

(I) Anomalies of origination and course: absent left main coronary artery (LMCA) (split origination of left anterior descending (LAD) and circumflex coronary artery), anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (high, low or commissural take off of the coronary artery), anomalous location of coronary ostium outside normal coronary sinuses (right posterior aortic sinus, ascending aorta, left ventricle (LV), right ventricle (RV), PA, aortic arch,

Table 1 The search strategy summary

Items	Specification
Date of search	2nd November 2023
Databases and other sources searched	PubMed
Search terms used	"coronary artery anomaly" "anomalous coronary [MeSH]", "anomalous origin of coronary artery", "anomalous aortic origin of coronary artery", "AAOCA", "anomalous pulmonary origin of coronary artery", "anomalous left coronary artery from pulmonary artery", "ALCAPA", "anomalous right coronary artery from pulmonary artery", "ARCAPA"
Timeframe	From 01/01/1960 to 31/10/2023
Inclusion and exclusion criteria	Inclusion criteria: case reports, case series, registries, observational and experimental trials; reviews; adult and pediatric population; English and French language
	Exclusion criteria: acquired coronary diseases; non-English and non-French publications
Selection process	Research and selection of relevant publications was conducted independently by M.E. and G.P.
	Selected studies were reviewed and disagreements resolved by M.C.

Table 2 Classification of coronary artery anomalies

Classification	Typology
(I) Anomalies of origin	(I) Absent LMCA
	(II) Coronary ostium near proper sinus (high, low or commissural take off)
	(III) Coronary ostium outside normal coronary sinuses (PA, ascending or descending aorta, aortic arch or epiaortic vessels, internal mammary artery, bronchial artery, LV, RV)
	(IV) Coronary ostium at improper sinus (R-AAOCA, L-AAOCA, circumflex CA or LAD from right coronary sinus)
	(V) Single CA
(II) Intrinsic coronary anomalies	(I) Congenital ostial stenosis or atresia; CA ostial dimple
	(II) CA ectasia or aneurysm
	(III) Absent CA
	(IV) Hypoplastic CA
	(V) Intramural CA (muscular bridge) or subendocardial CA course
	(VI) CA crossing
	(VII) split RCA or LAD
(III) Anomalies of termination	(I) Inadequate ramifications
	(II) CA fistulas (from RCA, LCA or infundibular Cas to RV, RA, coronary sinus, superior vena cava, PA, pulmonary vein, LA, LV, multiples sites)
(IV) Anomalous anastomotic vessels	–

LMCA, left main coronary artery; PA, pulmonary artery; LV, left ventricle; RV, right ventricle; R-AAOCA, right anomalous aortic origin of coronary artery; L-AAOCA, left anomalous aortic origin of coronary artery; CA, coronary artery; LAD, left anterior descending; RCA, right coronary artery; LCA, left coronary artery; RA, right atrium; LA, left atrium.

innominate artery, right carotid artery, internal mammary artery, bronchial artery, subclavian artery, descending thoracic aorta), anomalous location of coronary ostium at improper sinus [right coronary artery (RCA) that arises from left anterior sinus [right anomalous aortic origin of coronary artery (R-AAOCA)], LMCA that arises from right anterior sinus (L-AAOCA), circumflex coronary artery that arises from right anterior sinus, LAD that arises from right anterior sinus], single CA;

(II) Anomalies of intrinsic coronary arterial anatomy: congenital ostial stenosis or atresia, coronary ostial dimple, coronary ectasia or aneurysm, absent coronary artery, coronary hypoplasia, intramural coronary artery also known as muscular bridge, subendocardial coronary course, coronary crossing, anomalous origination of posterior descending artery from the anterior descending branch or a septal penetrating branch, split RCA, split LAD, ectopic origination of first septal branch;

(III) Anomalies of coronary termination: inadequate arteriolar/capillary ramifications, fistulas from RCA, LCA, or infundibular artery to: RV, right atrium (RA), coronary sinus, superior vena cava, PA, pulmonary vein, left atrium (LA), LV, multiples;

(IV) Anomalous anastomotic vessels (1,3).

Accordingly, to the current literature, the anomalies of origination and course seems to be the one with the higher clinical impact.

Anomalous coronary artery originating from the PA

The first knowledge of anomalous coronary artery arising from the PA (ACAPA) came from 1865 and 1885; when Krause and Brooks reported for the first time the existence of extra arteries arising from the PA and binding to CAs branches normally originating from the aorta. Later on,

from 1933, it has been known as Bland-White-Garland syndrome and the autoptic findings included a dilated and aneurysmatic RCA originating from the posterior side of the PA that gives off branches anastomosed with venous-like vessels running in the territory of the LCA (4). The morphological spectrum of ACAPA accounts for four different variants: (I) anomalous LCA from the PA (ALCAPA), (II) anomalous origin of the RCA from the PA (ARCAPA), (III) anomalous origin of both CAs from the PA, and (IV) anomalous origin of the circumflex artery from the PA. Only a minority of cases of anomalous origin of both CAs or an "accessory" artery from the PA have been reported, ALCAPA and ARCAPA remain the most frequent and clinically important (5,6). The true incidence of ARCAPA remain unknown, due to their possible asymptomatic course; the incidence reported in literature depends on a study conduit on patients undergoing coronary angiography and in around 0.002% (7). ARCAPA is slightly predominant in male in comparison with ALCAPA with a predominance of females above 2:1 (5,8). The incidence of ALCAPA is 1/300,000 live births, representing 0.24% to 0.46% of congenital cardiac disease (7,9,10). The anatomy of ALCAPA can be variable, the most common form is characterized by an anomalous CA originating from the left or the posterior sinus of Valsalva of the PA that gives branches (LAD and Cx) along its path. Clinical manifestations are generally in the first year of life, hence it is unusual to diagnosis in adult age. In adult presentations collateral circulation is more represented. Sudden cardiac death (SCD) among untreated adult with ALCAPA, accordingly with an early autoptic study, occurs at 35 years old on average; hereby surgery is required in all adult patients (11,12).

Pathophysiology and clinical presentation

The origin of one CA from the PA may be well tolerated in fetal and early neonatal life since PA pressure (PAP) are even with systemic pressure, this condition conduct to sufficient anterograde flow in both CAs. In the first month of life, the PAP reduces and, at the same time, the flow in the anomalous CA reduces and eventually reverses; when it happens, it will lead to myocardial ischemia (MI) and infarction. The reverse flow through the CAs causes a left-to-right shunt which will lead to volume overload, on the long-term; the left-to-right shunt is called the steal phenomenon. The severity of MI depends on the development of collateral circulation between the RCA and LCA while PAP gradually decreases.

Due to their different pathophysiology, the adult and infant group has different clinical presentations and prognosis. The infant group collects patients without collateral vessels; the adult group collects those with well-established collateral vessels. In the infant presentation, about 8 weeks after birth, the flow in the anomalous CA reverse and the lack of adequate collateral vessels imply a limited blood supply to the myocardium which cause MI; MI is the explanatory base to congestive heart failure (HF) and mitral regurgitation (MR) in these patients (10). In adult presentations, chronic LV subendocardial ischemia may develop due to limited blood supply to the myocardium, despite the presence of relevant collateral circulation.

Clinical presentation of the infant group in characterized by failure to thrive, profuse sweating, dyspnea, pallor, and chest pain while eating or crying. 90% of patients die within weeks or months of life without surgical repair (8,13). The most common symptoms of presentation in the adult group are the ischemic ones like angina, dyspnea, palpitations, or fatigue (66% of patients); followed by arrhythmic ones as ventricular arrhythmias (VAs), syncope, or SCD (17% of patients); and only a minority remain asymptomatic until adulthood (14% of patients) (8,13-15). About 62% of patients with life-threatening presentations had no antecedent symptoms. Patients with ARCAPA may be asymptomatic in the 38% of cases, with an incidental diagnosis; angina may be the symptom of presentation in 22% of cases, followed by dyspnea (17%), HF (10%) or SCD (2.7%) (5).

In the scenario of CAs originating from PA, the rarest condition is both CAs arising from the PA. Few days after birth the first symptoms ensues and death follows within two weeks; it is compatible with life only if associated with pulmonary hypertension (10).

Occasionally other congenital anomalies are described as associated with, might be of interest the abnormalities associated with ARCAPA which are quite common like aorto-pulmonary window (10.8%), ventricular septal defect (6.3%) and atrial septal defect (4.9%) (5,8).

Diagnosis

The diagnosis should always start with a thorough anamnesis and physical examination: in newborn and toddler it is necessary to investigate for typical symptoms of HF like failure to thrive due to lack of appetite, falling

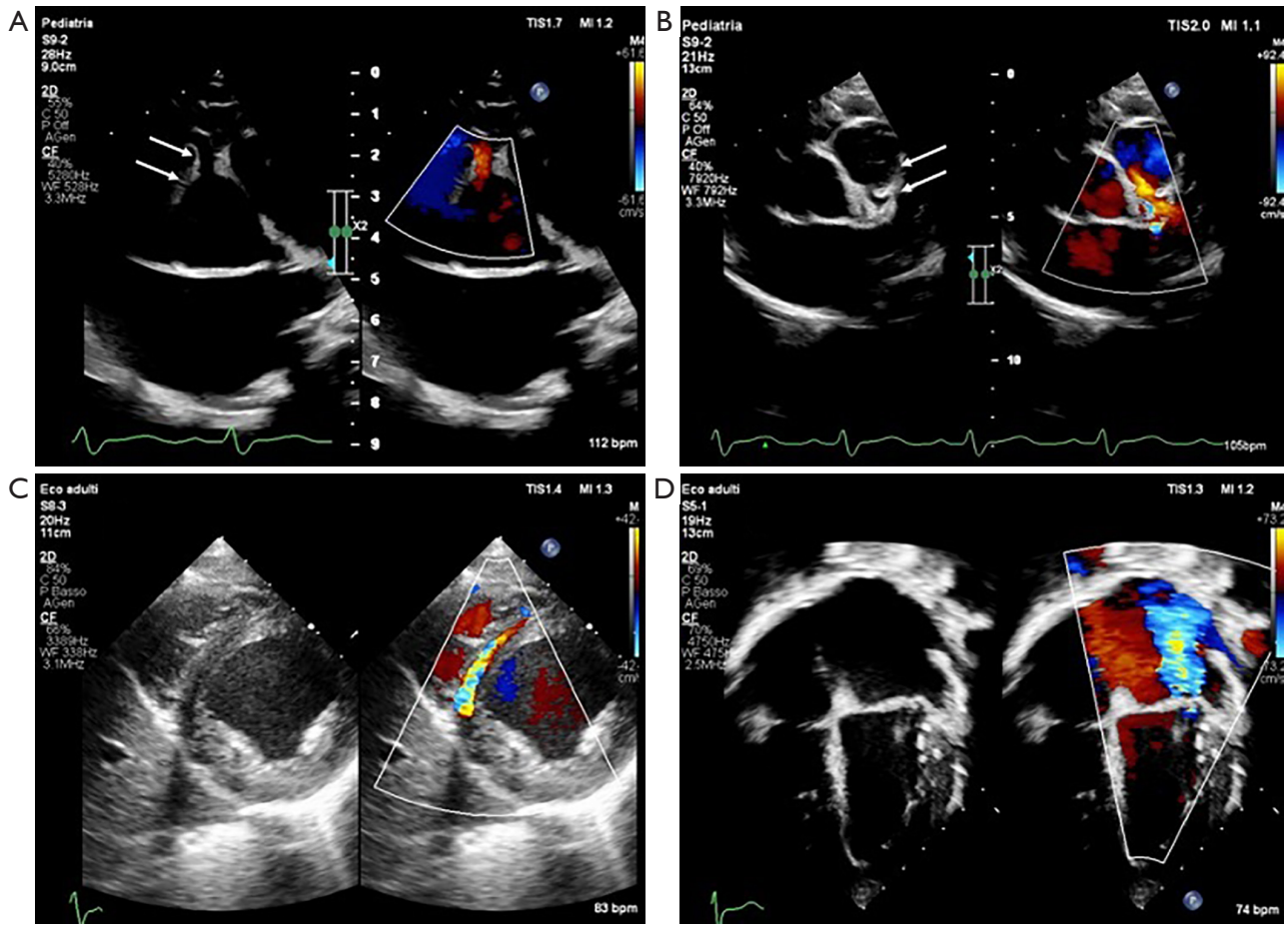

Figure 1 Transthoracic echocardiography of ALCAPA. Panel (A) shows a short axis view of the aorta with a mildly dilated RCA highlight by the arrows. Panel (B) is a short axis view modified to show the pulmonary valve en-face with the LCA arising from the PA (highlight by the arrows). Panel (C) shows the increased blood flow through the coronary artery in the middle of the interventricular septum due to steal phenomenon. Panel (D) is a four-chamber view that show severe mitral regurgitation due to fibrotic changes of papillary muscles. ALCAPA, anomalous LCA from the PA; RCA, right coronary artery; LCA, left coronary artery; PA, pulmonary artery.

asleep when feeding or becoming too tired to eat, excessive sweating while breastfeeding, irritability (grouchiness). Sometimes patients remain asymptomatic until adolescence when they become symptomatic for typical chest pain or, unfortunately, for SCD. Physical examination is characterized by the presence of a systolic or continuous or "to-and-fro" murmur, predominantly audible at the apical region and at the left sternal border (87% of patients). Newborn and toddler, if HF has ensued, will present dyspnea, tachypnea, polypnea, subcostal retractions, nasal flaring or grunting, rales.

The electrocardiogram (ECG) commonly presents MI patterns with Q-waves (50%), or it may show LV hypertrophy (28%) or left axis deviation (15%), in only a minority of cases it is normal (4%) (8).

Noninvasive diagnosis of anomalous CAs has always been demanding but the growing expertise and the progressive development of echocardiography have led to a continuous increased in the detection rate if performed by trained operator (16,17). Recently, have been described echocardiographic markers of ALCAPA, identifying specific aspect of infant and adulthood presentation. In the infant type the most common markers are: mildly dilated RCA, notable fibrosis of papillary muscles, secondary fibroelastosis of endocardium, severe dilatation of LV, reduced myocardial contraction mainly of the anterior and lateral walls, severe LV systolic dysfunction (*Figure 1*). The prevailing aspects in the adult presentation are: noticeable

septal flow from collateral arteries and severely dilated RCA, without impairment of LV function nor dimension (17). In response to chronic MI, myocardial fibrosis with a maladaptive remodeling may ensue, resulting in dilatation and reduction of LV function (5,10,18). As a consequence of LV dilatation and functional impairment, secondary MR may develop. The underlying mechanism are the same of secondary MR: annular dilation, chordal tethering and papillary muscle fibrosis (19). In current literature, 90% of exams performed by transthoracic echocardiography (TTE) were able to identify abnormalities which lead to the diagnosis of ALCAPA (46% of the exams) or at least to the suspicion of AAOCA (44% of exams). Abnormal echocardiographic findings like MR and/or segmental ventricular dysfunction should always lead to a complete routine diagnosis in a tertiary center. Still, there is a 10% of patients without symptoms and echocardiographic findings. Few studies have analyzed stress test to identify ischemia with adequate ischemia detect rate, but there are even less data regarding its safety. Induced ischemia may be detected by stress ECG and stress imaging studies respectively in 85% and 87% of the cases. The development of cardiac computed tomography (CT) and magnetic resonance imaging (MRI) has improved noninvasive evaluation of the CA anatomy. CT and MRI may help to directly visualize the origin of LCA from the posterior wall of the PA in ALCAPA, to identify a dilated and tortuous RCA, and to follow the course of inter-coronary collateral artery in the interventricular septum or through the external wall of the heart. All imaging techniques may assess LV systolic function. The further advantages of MRI are of demonstrate and assess flow from the LCA into the PA, and to determine myocardial viability with delayed gadolinium enhancement (13,20,21).

Treatment and follow-up

ALCAPA and ARCAPA if untreated have a mortality rate up to 90%, surgical correction has excellent short and long term results, showing to be effective and resolutive in restoring a two CAs circulation (20-24). Surgical indication is the diagnosis by itself, the current standards include urgent surgical repair soon after diagnosis with restoration of a dual CAs circulation, regardless of age (3,13,25). In fact, in neonates or infants, as well as in adult population, the surgical treatment is lifesaving and the best results are achieved with the availability of postoperative mechanical assist devices, whenever necessary (8,13,15,24,26). The postoperative use of mechanical assist devices ranges from 25 to 36% of cases (23,24,26). Less malignant variant like ARCAPA and single LAD or Cx arising from the PA are significantly rarer than ALCAPA, but they are also underdiagnosed due to the absence and negligibility of symptoms. However, to the state of the art, surgery should always be considered upon the diagnosis for all these variants (27,28).

Several surgical techniques have been described: ligation od the anomalous CA, various forms of coronary artery bypass grafting (CABG), subclavian artery graft, intrapulmonary baffle and direct coronary reimplantation to the aorta (8,13,18-20,21,26,28-31). Direct reimplantation of the CA is the techniques of choice whenever feasible, the discriminant for the choice is the position of the anomalous CA. When CA originates from the posterior side of PA, i.e., from a pulmonary sinus facing the aortic wall, direct anastomosis with mobilization of the LCA is the simplest and best choice (18,30). On the contrary, Takeuchi-type repair is the best surgical option in case the LCA arises from the left side of the PA. In that case the continuity between the CAs and the aorta will be obtained with a baffle (30,31).

CABG with ligation of the origin of the anomalous CA should be considered only for adult patients, in case of technical issues or presence of associated coronary artery disease (CAD) (8,28).

Early mortality rate after ACAPA correction range from 0% to 16% in current literature (5,22,31). A constant risk of SCD remains after hospital discharge and is directly related to the entity of residual fibrosis and ischemic scar in the LV. Indeed, the principal cause for SCD are the onset of malignant VAs and the substrate for VAs is the presence of areas of ischemic myocardium. Luckily, LV function recovers to almost normal after several months from the correction in most cases (6,11,12,18). The treatment and the timing of treatment of MR remains controversial: in the majority of patients MR is considered reversible and as a result should not be addressed at the time of correction surgery; in addition mitral valve surgery during ALCAPA correction would prolong the ischemic time and could be potentially harmful (18,19,24,32). However, significant MR persists in at least one third of patients, despite good recovery of LV function (24,26,29). This usually reflects the presence of irreversible papillary muscle infarction and scarring (24). Even though surgical results are satisfactory, a small risk of postoperative complications persist, the most alarming one are: MI due to anastomosis stenosis, aortic valve or pulmonary valve lesion (18,28). In literature are

Table 3 Anatomical high risk features of anomalous aortic origin of coronary artery

Anatomical features	Risk stratification
Ostial morphology	Round to slit-like morphology:
	• Round
	• Oval
	• Slit-like
	Proximity of ostium:
	• Non-confluent ostium
	• Joining ostia
	• Single ostium (bifurcation through the aortic wall)
	• Single ostium (bifurcation outside the aortic wall)
Take off angle	Exit angle =90°
	Exit angle <90°
	Exit angle <45°
Course of the coronary artery	Pre-pulmonic
	Retro-aortic
	Inter-arterial
	Trans-septal
	Retro-cardiac

reported few cases of RV outflows tract obstruction after Takeuchi repair (6,29,33,34).

Although early diagnosis and prompt surgical intervention lead to excellent results, the possibility of postoperative complications and the intrinsic risk for SCD necessitates long-term follow-up (19,29,30). Nowadays, there are no specific indication on the clinical and instrumental follow-up of these patients. Both first line imaging, with TTE, and second line imaging with cardiac CT and/or MRI should be used for long-term follow-up. TTE is useful to evaluate myocardial function as well as the evolution of MR through the time. In case MR persist or worsen, reoperation is required to reduce mitral valve insufficiency and its impact on LV dysfunction (18,28,29). MRI allows functional assessment and evaluation of MI, viability and fibrosis (8,13). Cardiac CT may be helpful to evaluate the anastomosis between the CA and the aorta or, in case a Takeuchi-type repair, the anastomosis of the baffle with the CA and with the aorta. Coronary angiogram should be considered as the techniques of choice in patients with typical or atypical symptoms of MI and in case the results of coronary CT scan show any abnormalities or are doubtful (35).

Anomalous aortic origins of the coronaries

Due to their progressively increasing clinical importance we are going to focus our attentions on AAOCA from the opposite coronary sinus. AAOCA has an incidence of 0.64% in newborn and of 0.17% in asymptomatic pediatric patients. This incidence is partially confirmed by post mortem analysis (0.3%); but increased up to 5.6% in patients undergoing coronary angiography (6,36,37). The R-AAOCA is 6 to 10 times more frequent than L-AAOCA, with a respectively incidence of 0.92% and 0.15% (38). The morphological features of these anomalies are of crucial importance to the clinical presentation and are represented by: the morphology of the ostium, the angle of take off of the CA and the course of the CA (*Table 3*).

The ostia of the CA can be sorted based on shape and diameters as: normal also called round (the transverse and the antero-posterior diameters are equals), oval (transverse diameter range between 50% and 90% of the antero-posterior diameter), slit-like (when the transverse diameter is <50% of antero-posterior diameter). When the CAs originates nearby to each other, it may be useful to describe the ostia using a four-level grading system: two distinct non-confluent ostia originating from the same sinus, two joining ostia located closed to each other, single ostia bifurcated in the aortic wall, single ostia bifurcated outside the aortic wall (*Figure 2*) (39,40).

The anatomic origin of a normal CA is distinguished by an exit angle roughly equal to 90°. When the orifice is abnormally angulated, the CA passes obliquely through the aortic wall and the exit angle is established by the length of course of the CA in the wall: if the exit angle ranges between 45° and 90° there is an angulated origin of the CA without a truly intramural course; if the exit angle is <45° the length of the intramural tract is greater than the diameter of the CA leading to a lower exit angle with a longer intramural course (*Figure 3*). The longer the intramural tract is, the more it is subject to intraparietal compression during acute systolic blood pressure increment, as in arduous physical activity (41) Proximal diameters are habitually smaller than the distal diameters, therefore juxta-aortic narrowing exceeds the intramural course in the majority of cases.

In AAOCA from the opposite coronary sinus the CA has five potential paths to its perfusion territory:

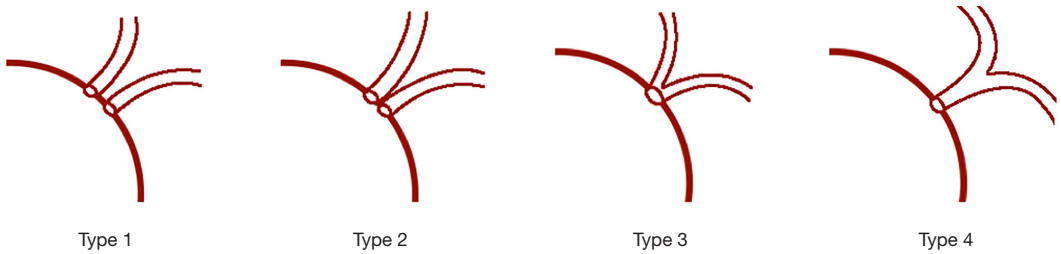

Figure 2 Four-level grading system of coronary artery origins. Type 1: two separate non-confluent orifices arising from the same sinus. Type 2: two confluent orifices located adjacent to each other. Type 3: single orifice with bifurcation in the aortic wall. Type 4: single orifice with bifurcation outside the aortic wall.

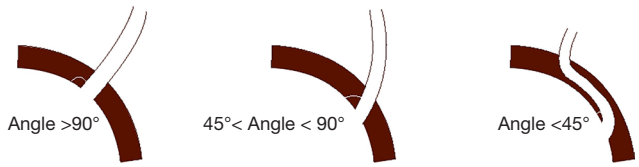

Figure 3 The exit angle of a normal CA is approximately equal to 90°, when the coronary vessel passes obliquely through the aortic wall there is an abnormal angulated orifice. If the exit angle ranges between 45° and 90° there is an angulated origin of the CA without a truly intramural course; if the exit angle is <45° the length of the intramural tract is greater.

(I) Pre-pulmonic: anterior to the RV outflow tract, usually involves the LCA;
(II) Retro-aortic: posterior to the aortic root, passes into the space between the posterior sinus of Valsalva and the interatrial septum. Usually involves LMCA or left circumflex (LCX) artery from RCA or right sinus of Valsalva;
(III) Inter-arterial: between the aorta and PA;
(IV) Trans-septal: it takes a subpulmonic course, traverses the interventricular septum inferiorly and anteriorly and takes an intramyocardial course, coming out at its normal epicardial position after giving origin to septal branches. LAD or LMCA are the CAs most frequently involved;
(V) Retro-cardiac: the path of the CA is in the posterior AV groove, behind mitral and tricuspid valves (42).

Being described in the 0.26% of the population, the retro-aortic course is the most common path (43).

The current literature has reported that the length of the intramural course (44-47) the presence of an elliptic shape (defined as antero-posterior diameter/latero-lateral diameter ratio of >1.3) of the proximal vessel and its length is associated with an increased risk of MI (48). New evidences have shown that myocardial mass as well as other contributing factors (e.g., volume status and type of physical activity) impact on the hemodynamic relevance of CAs anomaly (49,50). However, in few cases have been reported that ischemia is not correlated independently with any of specific anatomic features (49).

Pathophysiology and clinical presentation

The most well-known pathophysiological aspect of AAOCA is MI, but the underlying causes of this pathological aspect are still questionable in consideration of the highly variability of the different anatomic high-risk characteristics. Pathological evidence of acute MI and/or of chronic MI with fibrosis have been reported in literature. Hence, has been hypnotized that MI could take place in infrequent bursts, which became cumulative over time. Multiple ischemic burst may cause patchy myocardial necrosis and fibrosis, which might create myocardial re-entrant and lead to unstable VAs (51). Since the interarterial course is associated with an increased risk of SCD, it has been considered the main determinant of MI, assuming a scissor-like interruption of the coronary blood flow, especially during physical activity, due to the nearness of the interarterial segment to the aorta and the PA. Nevertheless, taking into consideration the pressure in both circulatory systems, it is improbable that the PA with its low-pressure system develops substantial counterforce to occlude the anomalous CA with its higher-pressure. On the other hand, the anomalous CA frequently pass through the thickness of the aortic wall, hence, the interarterial tract may rather act as an index for the anatomic high-risk features. Several potential mechanisms have been proposed to explain ischemia: the acute angle of take-off of the anomalous CA,

which may be kinked and developed a more acute angle of take-off during exercise due to expansion of the aortic root and PA, decreasing the luminal diameter; the slit-like orifice of the CAs associated with a flap-like closure of the ostium; the intramural course of the CAs and its length, which may be associated with lateral compression of the CAs but also to intrinsic hypoplasia of the CA which cannot grow normally either before or after birth; spasm of the ACA, possibly as a result of endothelial injury; and the concurrent present of ventricular hypertrophy, the increased myocardial mass demand an increased myocardial supply (1,44-50). The latest hypothesis is that the longer the intramural tract is, the more it is subject to intraparietal compression during acute systolic blood pressure increment, as in arduous physical activity, and therefore the higher is the risk of prolonged coronary occlusion (41).

The leading pathophysiological mechanism to MI have been grouped in

- Fixed features: slit-like ostium, proximal narrowing;
- Dynamic features: acute take-off angle, elliptic shape vessel, intramural course and coronary spasm (41).

The MI associated to AAOCA has a wide spectrum of presentation: from complete asymptomatic to SCD, with all the possible presentation in between: typical or atypical chest pain, palpitations, dizziness, breathlessness or syncope. All the symptoms associated with AAOCA are quite common in the cardiological clinical practice and are suggestive of MI, therefore, they should be considered as the tip of the iceberg of this pathology. Some cases are asymptotic and the diagnosis may be incidental throughout instrumental examination. Current literature reports that only one third of patients with SCD due to AAOCA previously presented with cardiac symptoms (41,52).

According to multiple registry, AAOCA are the second most common cause of SDC, especially in younger patients (under 30 years of age) and in athletes (commonly during physical activity). Among AAOCA, R- or L-AAOCA are the most frequent cause of SCD and aborted SCD (50-55). Brothers at Al. have estimated a cumulative risk of SCD over a time of 20 years in competitive athletes of 6.3% in the presence of L-AAOCA and of 0,2% in case of R-AAOCA (55).

Diagnosis

The diagnosis of AAOCA may be suspected by clinical presentation, but must be confirmed. The diagnostic tool of choice for the screening must be noninvasive, relatively low cost, widely available, with high sensitivity and if possible high specificity. TTE is a common noninvasive tool used to evaluate suspected or known cardiac disease in young patients. As a noninvasive, rapid, and widely available test with low cost; TTE is the perfect screening exam. TTE has a high feasibility and accuracy for the evaluation of CAs origin as well as their proximal tracts, however, some limitations exist (*Figure 4*). TTE depends on patient habitus for optimal image quality and on the experience of the operator. The incidence of AAOCA diagnosed with echocardiography varied from 0.09% to 0.39% (up to 0.76%) which is lower than the one diagnosed by CT (0.3–1.8%) or by coronary angiography (5.6%), but near to the one diagnosed on post mortem analysis (0.3%) (6,36,50,56). Echocardiographic views for the evaluation of AAOCA have not been standardized. The screening of AAOCA by TTE is feasible and accurate when appropriate examinations are performed by experienced operator; however, specific acoustic windows and definitions of defects other than AAOCA need to be standardized to improve sensitivity and specificity (43,56). Stress echocardiograms, knowingly applied in adults with special focus on CAD, have not been used much in the pediatric population, and published studies are relatively scarce. Giving the progressively increased used of stress echocardiograms in different situations (like Kawasaki syndrome, transplanted hearts, cancer cardiology and evaluations after heart surgeries with coronary artery reimplantation), it is highly probable that stress echocardiograms would become more and more used in the next feature, but currently there are no clear data about its use. When TTE is not diagnostic, or when the diagnosis of AAOCA has been performed (the spatial resolution of TTE is limited, therefore AAOCA specific characteristics and the ones of the contiguous structures are difficult to be defined), it is desirable to complete the diagnosis with more invasive tools. The choice between CT and MRI depends on multiple factors as availability, local expertise and the specific features of these tools. Due to high spatial resolution, rapid scan times, lower costs and its ability to characterize multiple anatomic high-risk features of AAOCA; CT is preferred in multiple centers. Rapid imaging acquisition by free-breathing means that the exams may be performed without sedation in selected pediatric cases. The positive aspects of MRI is that without radiation or iodinated contrast agents provides CAs anatomical characteristics and functional imaging; the negative aspects are lower spatial resolution, increased scan times, and higher cost. Free-breathing MRI allows to visualizes the coronary takeoff and course in nearly all patients when

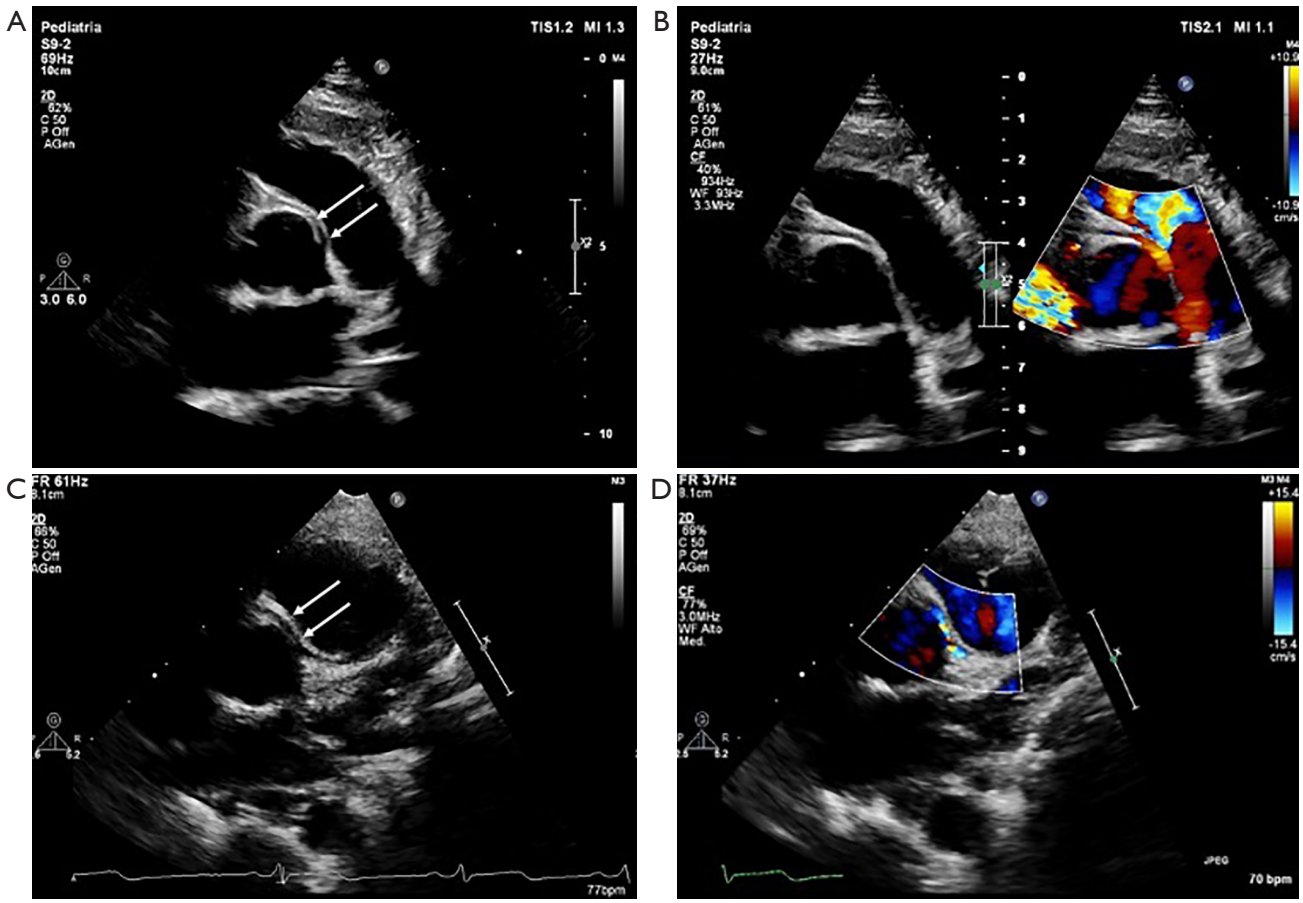

Figure 4 Transthoracic echocardiography of R-AAOCA and L-AAOCA. Panel (A and B) show the RCA originating from the left coronary sinus with an interarterial and an intramural course. Panel (C and D) show a LCA arising from the right coronary sinus. In this last case it is extremely difficult to identify the precise origin of the LCA, but it is possible to suspect the diagnosis due to the position of the coronary artery and the peculiar color doppler. RCA, right coronary artery; LCR, LEFT coronary artery. R-AAOCA, right anomalous aortic origin of coronary artery; L-AAOCA, left anomalous aortic origin of coronary artery; RCA, right coronary artery; LCA, left coronary artery.

performed by experienced center, but sedation is required in the majority of young children (e.g., <7 years of age) (43). Cardiac MRI may asses myocardial perfusion detecting MI with excellent sensitivity and specificity in the adult population and with good results in the pediatric population (57-60). Dobutamine stress MRI while mimic exercise by the infusion of dobutamine (agent that increases myocardial contractility while decreasing systemic vascular resistance) allow the operator to asses myocardial perfusion at rest and at peak of mimed exercise.

In selected cases, to complete the diagnosis, it may be necessary to perform an invasive exam. Normally, invasive coronary angiography (ICA) is a widely available technique which offers high spatial and temporal resolution with low risk; combined with intravascular ultrasounds (IVUS) offers excellent dynamic imaging. IVUS offers a precise sequential visualization of the transversal lumen and wall of the CA, with superior resolution to ICA throughout the cardiac cycle. Angelini and his group have published multiple study on the use of IVUS on AAOCA identifying three major aspect to asses with IVUS:

- Hypoplasia index: the juxta-aortic tract of the CA is smaller in circumference than the distal extramural tract. The hypoplasia index is the ratio between the circumference of the intramural vessel and the circumference of the more distal portion.
- Asymmetry ratio: due to lateral compression, the cross section of the intramural portion is peculiarly not circular but ovoid. The asymmetry ratio is the ratio of the smallest to the largest diameter

in an IVUS cross section. During the systole, the smaller diameter is further compressed, leading to intermittent worsening.

- ❖ Stenotic segment length: as in any coronary stenosis, the segmental length is another measure of severity (1).

Engaging AAOCA ostia during an IVUS study may be triggering due to the presence of ostial narrowing, ostial ridge or acute angle of take-off. Differences CA spasm from true narrowing is of crucial importance during IVUS (61).

Increasing interest is developing for invasive functional evaluation with fractional flow reserve (FFR) and with instantaneous wave-free ratio (IFR). Both methods have been initially used to asses obstructive CAD in adult population which give them utility assessing the fixed component of AAOCA. Correspondingly, evaluation should be performed similarly to patients with CAD, including measurement of the pressure gradient over the anomalous segment. On the contrary, anatomic aspects of the dynamic component (which may represent the main driver of MI in AAOCA) gain hemodynamic relevance only during exercise. Of note, pharmacologic vasodilatation cannot assess the dynamic components, as it requires an increased cardiac output with subsequent augmented vessel wall stress of the aorta. These exercise-induced adaptations can provoke a lateral compression sufficient to cause MI (even during diastole). Therefore, physical stress or positive-inotrope/positive-chronotrope protocols including volume infusion to mimic strenuous exercise are needed to depict ischemia by dynamic compressions (62).

Due to their significantly different clinical impact, recently, has been proposed to classify AAOCA accordingly to their intrinsic risk and need for additional testing and risk stratification. The AAOCA have been grouped as: low risk (there is no necessity for further evaluation), unclear risk (based on each case, evaluate the necessity for additional risk stratification), and high risk (intervention is usually recommended) (63).

The low risk grouped anomalies considered benign variants of normal coronary anatomy and are not associated with symptoms or adverse clinical events. This category is not associated with impairment of coronary flow or MI and do not present a higher prevalence in autoptic study of young patients with SCD. Separate ostia of the LAD and Cx artery, split RCA, high origin of the RCA from the right coronary sinus, origin of the Cx from the RCA or from the right coronary sinus taking a retroaortic path and small coronary artery fistula (CAF) are all examples of low risk AAOCA. AAOCA from the opposite coronary sinus with prepulmonic, retroaortic, retrocardiac, and subpulmonic path may be considered with benign courses and, therefore, at low risk. In those situations, there is no necessity for treatment. However, when atherosclerosis develops a part of cases might present with early symptoms or increased risk of complications. Predominantly, the need for additional testing is restricted to these very selected cases.

R-AAOCA with interarterial course, myocardial bridge and medium to large CAFs should be classified as unclear risk. The unclear risk group is the most challenging one and require a specific risk stratification to choose the appropriate treatment due to the highly variability between clinical events, MI and symptoms. In such instances, both noninvasive and invasive tools should be used on an individual basis to assess the risks and benefits of surgical treatment. The majority of SCD take place in patients younger than 35 years old, normally during or shortly after strenuous exercise, but VAs may arise at any age; therefore, clinical data including patient age and symptoms are essential to the risk stratification in AAOCA. As a matter of fact, exertional angina or syncope are risk factors for adverse outcomes, since they are indicative of MI. The noninvasive tools in the assessment of the risk of these patients are: resting ECG, TTE and stress tests. Anatomic features of AAOCA are best evaluated by CT or MRI. Although CT may precisely identify several anatomic features, the dynamic component of intramural systolic compression is missed. In this context, the use of IVUS and the measurement of FFR during coronary angiography has been incorporated to the evaluation of AAOCA, allowing quantification of coronary stenosis secondary to intramural compression during both systole and diastole. In the perspective to incorporate IVUS and FFR as stratification tools there is a lack of data to identify the optimal threshold associated with symptoms, clinical events, and improvement after intervention. At the moment, surgical treatment should be chosen for patients with symptoms, evidence of MI, or high-risk features on either CT, IVUS, or FFR. R-AAOCA is a more frequent condition in clinical practice than in autoptic study due to SCD which should lead us to conclude that is associated with adverse outcomes in a minority of patients. In this scenario, the above mentioned clinical and imaging characteristics are useful to evaluate the benefits and the risks of surgery versus noninvasive treatment.

L-AAOCA is at high risk and is a compelling indication for intervention. The clinical presentation may be an aborted SCD as well as symptoms of MI or VAs. Nowadays, there is a lack of prospective data to delineate the natural

history L-AAOCA, however, there is a disproportion in autopsy studies and is contemplated to be a paramount cause of SCD. In such instances, there is no evidence that noninvasive tests are accurate to evaluate MI, and the clinician should not be reassured by a negative test as a sing of favorable prognosis. Although promising, the utilization of IVUS and FFR to evaluate the intramural segment, the degree of stenosis, and the coronary flow reduction in patients with L-AAOCA is an area in continuous development, but there is a lack of data correlating findings on invasive evaluation and patient outcomes (39,64). Irrespective of symptoms or evidence of MI, the diagnosis of interarterial L-AAOCA is normally considered an indication for surgery (63).

Treatment and follow-up

The treatment is surgical, but indication to surgery is still controversial and vary among specific AAOCA. Factors that should be taken in to consideration are symptoms of MI, like typical chest pain, breathlessness and extensional syncope; and signs of MI at rest or during stress test through functional imaging. The last aspects that should be taken into consideration is the age of the patients, AAOCA are rarely dangerous before ten years of age and later than 35 years of age. According to the ESC guidelines for the management of adult congenital heart disease of 2020 surgery is recommended for AAOCA from the opposite coronary sinus in patients with typical angina symptoms who present with evidence of stress-induced MI in a matching territory or with high-risk anatomy. Surgery should be considered in asymptomatic patients with R-o L-AAOCA with evidence of MI or with L-AAOCA without evidence of MI but with high-risk anatomy. At last, surgery may be considered in asymptomatic patients with L-AAOCA without evidence of MI or high-risk anatomy if younger than 35 years of age and for all symptomatic patients with AAOCA regardless of MI o high-risk anatomical features. The only controindication to surgery is R-AAOCA in asymptomatic patients without evidence of MI or high-risk anatomical features (25).

Several surgical techniques have been proposed and used based on the anatomic features of the CA: unroofing of the intramural course of the CA, neo-ostium creation, translocation with reimplantation of the CA and CABG. The unroofing of the intramural course of the CA is, by definition, the treatment of choice for AAOCA with intramural course but should be preferred by CA translocation in case the intramural tract course under the aortic valve. Neo-ostium creation can provide more complete elimination of the interarterial course. Neo-ostium creation which consist in creating a coronary ostium at the correct anatomic position for each CA, can be applied to either L- or R-AAOCA. This technique involves lower risk of proximal CA stenosis or kinking than coronary artery translocation. CABG does not appear to be a good treatment method for young patients without proximal native CA stenosis because of concerns regarding graft patency due to competitive flow, and limited long-term durability of the graft in young patients. CABG should be considered in older patient, especially in presence of evidence of CAD. The most common complications after surgery are pericardial effusion and MI, much more rare, but greatly more severe. Patients that have undergone surgical treatment of AAOCA should be periodically test after surgery to evaluate long term results and new MI eventually developed after surgery (65).

CAAs in athlete

Only a minority of athlete with AAOCA present with typical signs or symptoms of MI, hence highlighting the need of a high clinical suspicion to achieve the diagnosis. Premonitory cardiac symptoms have been reported to occur shortly before SCD, suggesting that a positive clinical history requires to rule-out coronary abnormalities (51). The efficacy of the rest ECG as a screening tool may be improved using modern criteria for the interpretation of the ECG (66). Indeed, standard testing with rest or stress ECG are unlikely to demonstrate clinical evidence of MI and they would not be reliable as screening tests (51). For such reason, the presence of ischemic electrocardiographic abnormalities in competitive athletes, even with excellent workload capacities, in absence of cardiomyopathy, could be mainly determined by coronary anomalies and need to be further investigated (67).

The screening of AAOCA by TTE, as mentioned above, is feasible and accurate when the exam is performed by well-trained practitioners (68). Keeping that in mind, some limitations exist: the incidence of AAOCA at TTE series varies from 0.09% to 0.39% (up to 0.76%) and is lower than the one reported by CT series (0.3–1.8%) (56). CT not only increases the diagnostic efficacy, but also provides essential information for risk stratification and prognosis, playing a crucial role in the clinical evaluation and management of athletes (69). Management options for athletes with

AAOCA are complex and require a comprehensive clinical evaluation. As such, clinical management and sport eligibility decisions require an individualized approach (70). Currently, there is still lack of large studies or randomized control trials with prospective follow-up, which may help clinicians in the decision-making process; for this reason, the athletes and their parents or guardians should always be involved. In asymptomatic patients with AAOCA without interarterial course or high-risk anatomical features competition may be considered, after adequate counselling on the risks, provided there is absence of inducible MI. Patients with AAOCA with high-risk anatomical features should be discouraged to practice competitive sports. On the other hand, participation in sports may be considered 3 months after surgical correction if the athlete is symptom-free with a negative exercise stress test. However, to facilitate optimal sternal wound healing, it is advisable to abstain for at least 6 months. Tailored physical activity that mainly involves low to moderate intensity exercise might be considered during the convalescent and rehabilitation period, on a case-by-case basis in specialized centers (71).

Conclusions

CAAs represent one of the most appealing but still controversial topics in cardiology. The increasing knowledge of their characteristics and associated risks is giving progressively more clarity on the subject, even if multiple aspects remain unknown. The recent literature has tried to develop a comprehensive classification of CAAs taking into consideration all the possible coronary anatomic variations, independently from their clinical and hemodynamic impact. This review has focused on the most important CAAs in the pediatric population, based on a clinical perspective, to provide a comprehensive overview of their epidemiological and pathophysiological features, and possible clinical implications.

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