CORONARY ARTERY ANOMALIES: A 2020 REVIEW

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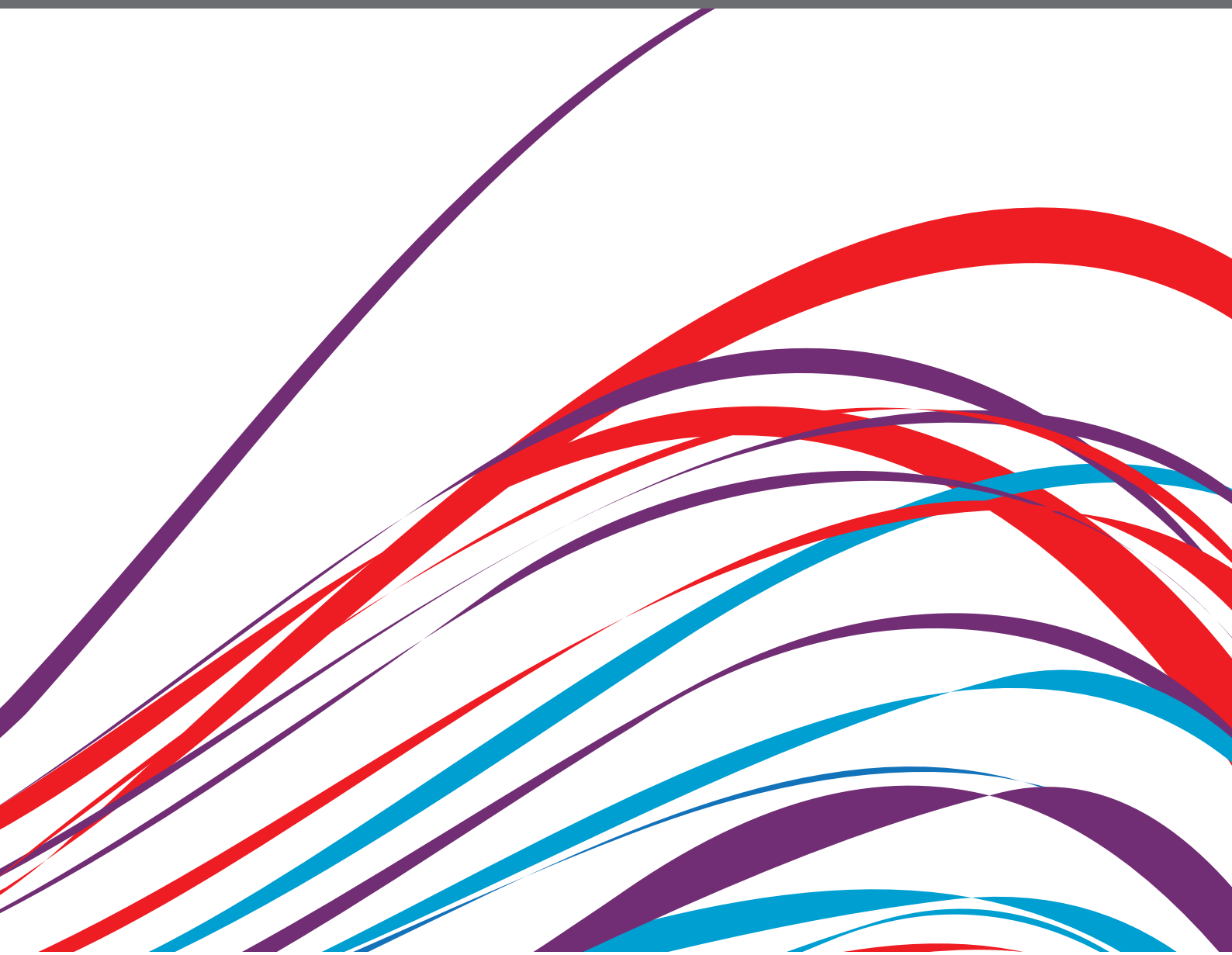

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CORONARY ARTERY ANOMALIES: A 2020 REVIEW

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EDITORIAL
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Editorial: Coronary Artery Anomalies: A 2020 Review

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Keywords: ACAOS, anomalous aortic origin of the coronary artery (AAOCA), coronary artery anomalies (CAA), anomalous coronary arteries originating from the opposite sinus of Valsalva, anomalous coronary arteries

Editorial on the Research Topic

Coronary Artery Anomalies: A 2020 Review

Coronary artery anomalies (CAA) are one of the remaining mysteries in cardiology. Currently, reports of an anomalous coronary vessel origin/and or course is rare (1), but with the increasing accuracy of the latest imaging technology, they may begin to be found more often. However, their clinical significance varies greatly across different variants (2, 3). The spectrum ranges from the hemodynamically relevant anomalous origin of the left coronary artery from the pulmonary artery (3) to benign coincidental findings of a superficial myocardial bridge. Within that range, the anomalous coronary artery from the opposite sinus of Valsalva (ACAOS) with an interarterial course (i.e., course of the anomalous coronary tract between the aorta and the pulmonary artery) often leaves treating physicians in the dark, as the anatomical presence of ACAOS does not automatically imply a risk for future events. In the 90's and 2000's, important data from autopsy studies were published, showing that CAA may represent the underlying cause of sports-related sudden cardiac death in certain circumstances (4, 5). However, as this does not reflect the risk of adverse cardiac events in a person living (mostly unknowingly) with CAA, more data are needed to accurately counsel and treat these patients in this clinical setting. Moreover, as invasive and noninvasive imaging becomes more relevant with consecutive increasing cases of CAA, evidence on optimal downstream testing and therapy is needed in order to tailor therapy. Lastly, despite the reported low surgical risk for most repair procedures for CAA, a real benefit in minimizing the sudden death risk has not been fully demonstrated yet. In this regard, this special section *"Coronary Artery Anomalies: A 2020 Review"* in Frontiers in Cardiovascular Medicine aims to address some of the major questions in the setting of CAA. We thank the authors for their eminent contributions and it is with great pleasure that we can present eight interesting articles on this important topic from different internationally recognized research groups in the field of CAA.

We congratulate the authors Thiene et al. and Rizzo et al., both from the University of Padua, for the two first articles. They nicely summarize the history, the embryology, and anatomical aspects of CAA by illustrating different aspects with historical pictures, excellent drawings, images from postmortem casts, and pathological specimens. The anatomy of subepicardial coronary arteries in normal hearts and its right, left, or co-dominance was first published in a milestone paper in 1903 by Antonio Banchi, an anatomist in Florence, and then confirmed by post-mortem casts in 1963 by Giorgio Baroldi and shortly after *in vivo* by Sones at the Cleveland clinic. From the embryology point of view, the supepicardial vessels derive from extracardiac epicardial cells, which form a plexus like vasculature secondary invading the myocardium and growing toward the aortic root to the facing aortic sinuses (Thiene et al.). During this process a misconnection to the wrong sinus

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of the Valsalva can occur, however, its exact pathological mechanisms seem to be still not well-understood. Four rare anomalies are nicely presented and discussed in different clinical settings in the articles published by Borns et al. and Tang et al.. One case was a 7-year-old girl diagnosed with a single left coronary ostium with a giant coronary trunk, coronary artery to right ventricle fistula, and coronary artery ring. The authors documented the case very well and it is the first described variant of its kind in the literature. The coronary fistula was surgically ligated with an off-pump strategy and the patient was discharged on day five post-operation and free of symptoms during the 3 years of follow-up (Tang et al.). The three other cases by Borns et al. were a 14 years old teenager with left ACAOS with acute chest pain and elevated troponin, a 15-year old girl with a right ACAOS with chest pain, and an 11 year- old girl with syncope after swimming and ventricular fibrillation and an anomalous origin of the left coronary artery arising from the non-facing sinus without an interarterial course, but with a short intramural course. Low-dose computed tomography with 0.38 mSv and 60 ml contrast or cardiac magnetic resonance imaging were used in these cases and seem to be the optimal anatomical imaging modality to exactly describe the anatomy. As all these cases presented with acute signs and symptoms of ischemia due to the underlying CAA, timely surgical correction was performed. The three cases showed an intramural course and therefore the surgical approach was unroofing (Borns et al.). Interestingly enough, in the case with an anomalous coronary artery originating from the non-facing (non-coronary) sinus without an interarterial course, a long (i.e., 1 cm) intramural course was confirmed intraoperatively and therefore it seems that the anatomical high-risk feature of intramural course has to be considered separately from the interarterial course and is not always linked to it. In this regard, Bigler et al. illuminate in a comprehensive and in-depth review the pathophysiology of different anatomical high-risk features of CAA and how hemodynamic relevance should be assessed. The concept of a fixed component, similar to the stenosis known from coronary artery disease (anatomic high-risk features of slit-like ostium and proximal narrowing) and additional dynamic component (acute take-off angle, intramural course with the elliptic vessel shape) is discussed. It is highlighted that patients with a CAA should not be invariably referred to direct surgery, but rather should undergo a thorough noninvasive and invasive assessment. This includes an anatomic description of the anatomy (best done with computed tomography or cardiac magnetic resonance) and additional functional testing with dobutamine/volume challenge under maximal heart rate (i.e., invasive fractional flow reserve evaluation and intravascular ultrasound imaging to depict the presence and extent of possible dynamic lateral compression) (Bigler et al.). However, the authors emphasize that besides the assessment of ischemia, one has to be aware of the possible presence of myocardial fibrosis and scarring (e.g., suspected to occur in anomalies as an expression of recurrent myocardial ischemia) which may serve as the substrate for ventricular tachyarrhythmia's, and has to be taken into account for risk stratification of patients with CAA. Regarding the optimal surgical approach, Padalino et al. elaborate a complete review on the various surgical techniques (coronary unroofing, osteoplasty, reimplantation, pulmonary artery translocation, coronary artery bypass grafting), which are usually devoted to a particular anatomical subtype of CAA. Although ideally, the coronary surgical reconstruction for CAA should normalize the anatomy, relocating the large ostium in the center of the appropriate sinus, reproducing a normal take-off angle, and eliminating any intramural or interarterial course, none of the current surgical techniques can address all of these components, and each is susceptible to individual technical pitfalls (Padalino et al.). To document and control treatment success, Meijer et al., propose a compelling imaging approach in their original study. In detail, 11 patients were retrospectively identified out of 54 consecutive patients who underwent surgical repair of CAA over a 17 year period at the Leiden University Medical Center, and who had pre- and post-operative computed tomography imaging available. The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of the operated coronary artery. To allow an accurate evaluation of the effective orifice area at diagnosis and after surgical repair introduced a new parameter—the coronary triangulated orifice area (CTOA). In fact, postoperatively, the median CTOA increased significantly from 1.6 mm^2 [IQR 0.9;4.9] to 5.5 mm^2 [IQR 3;11.8] ($p < 0.005$). During follow-up, in three patients restenosis of the operated coronary artery was suspected and in these patients the CTOA showed only a limited postoperative increase of $\leq$ 1.4 mm^2. This study highlights, that patients with CAA undergoing surgery should be closely monitored and possibly benefit from post-operative imaging to derive the new anatomic circumstances. Besides surgery, percutaneous coronary intervention (PCI) might be another alternative approach in selected patients with CAA. In an interesting overview by Aubry et al. the role of PCI in patients with CAA and interarterial course is presented and discussed. There is not much literature published on PCI in CAA so far, and we congratulate the authors for establishing the ANOCOR working group which, since 2014, has started a prospective registry of patients with right coronary artery anomalies and evaluated the outcome of those treated by PCI with stenting. The strengths of PCI are a shorter hospital stay and fewer post-procedural adverse events compared to surgery, however, long-term potency is not well-known and this approach might be rather a possible future strategy for older patients and not for younger adults or children. Furthermore, PCI may be a bail-out strategy to treat some surgery failures, such as acute occlusion or scarring stenosis (Aubry et al.).

To conclude, within the last decades we have gained important knowledge and evidence on coronary artery anomalies. However, large-scale prospective studies are still lacking, and hopefully, the efforts of in-depth systematic assessment of CAA like the NARCO (ClinicalTrials.gov ID: NCT04475289) and MuSCAT trials (6), and several multinational registries (7, 8) will provide a better understanding of CAA and its risks. Hopefully, the new evidence can help to guide physicians in the future toward the optimal selection of surgical candidates and adequate surgical techniques. This would reduce the incidence of adverse cardiac events, but also could help avoid unnecessary open-heart surgery in low-risk patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Symptomatic Coronary Anomalies and Ischemia in Teenagers – Rare but Real

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Three cases of teenagers with anomalous aortic origin of the coronary arteries (AAOCA) are presented with typical exercise induced symptoms (chest pain, syncope or dizziness). Using multimodal imaging, diagnoses was confirmed showing interarterial and/or intramural course of the coronary artery explaining the ischemia induced symptoms. Successful surgical correction with unroofing of the AAOCA was performed in all three cases with a favorable outcome. Even though AAOCA are rare, some variants may be relevant and potentially life threatening, therefore treating physicians should be aware of correctly diagnosing and treating these individuals.

Keywords: coronary artery anomaly, anomalous aortic origin of the coronary arteries, AAOCA, chest pain, interarterial, angina pectoris, teenager

INTRODUCTION

Anomalous aortic origin of the coronary arteries (AAOCA) is a rare but potentially life threatening congenital heart disease, especially in the young. Most frequently in this anomaly, the left coronary artery arises from the right-facing sinus or the right coronary artery arises from the left-facing sinus or either coronary artery originating from the non-coronary sinus. Depending on the subsequent course of the anomalous coronary artery, symptoms and relevance can vary. The danger being a fixed narrowing or a dynamic lateral compression of the coronary artery with subsequent myocardial ischemia. Most variants are benign anomalies with only rare reported cases of ischemia. Nevertheless, the subtype with interarterial and/or intramural course of coronary artery is associated with myocardial ischemia and sudden cardiac death (1). Typical symptoms are

exercise induced chest pain, dizziness or syncope, but in about half of patients with AAOCA its first presentation is sudden cardiac arrest (2). Using multimodality cardiac imaging aims to characterize the exact anatomy of the anomalous coronary artery and is a central part in the interdisciplinary decision-making toward surgical correction (3). Therefore, it is crucial to identify patients at risk, in order to provide optimal care prior to irreversible myocardial damage. Here, we present three cases of symptomatic teenagers with AAOCA, and explore the challenges we are facing when teenagers present with symptoms suggestive of AAOCA. Further, we show how multimodal imaging helped in diagnosing and the decision-making toward surgery and explore on the details of the surgical approach of unroofing.

CASE SERIES

Case 1

A 14-year-old teenager was admitted to our emergency department with exercise induced chest pain. While at the local swimming pool with his school and running multiple times a flight of stairs to the upper level, he developed chest pain, nausea and dizziness. When the ambulance arrived, he was in a hemodynamically stable condition and the pain slowly subsided. In the medical history, he reported two similar episodes within the last 6 month with acute chest pain and dizziness after strenuous exercise. Because of rapid improvement of symptoms after ceasing exercise, no medical care was sought following these earlier episodes. In rest conditions and under moderate physical exercise he was completely asymptomatic and he described himself as having a normal level of fitness. The further past medical history and family history was unremarkable.

At time of admission to the emergency department, the vital parameters were within the normal range. The ECG did not show any abnormalities. The laboratory tests showed an elevated high sensitive Troponin T (TroponinThs) of 309 ng/L (reference value $<$ 14 ng/L) and slightly elevated CK-MB of 5.9 μg/L (reference value $<$ 4.9 μg/L). In the echocardiography, a coronary artery anomaly was suspected, because the left coronary artery did not arise from the left-facing sinus and the presence of a coronary flow pattern arising from the right-facing sinus and continuing between aorta and pulmonary artery suggesting an interarterial course of the left coronary artery. Left- and right heart dimensions and functions were normal (**Figure 1**).

An ultra-low dose coronary computed tomography angiography (CCTA) with 0.38 mSv and 60 ml contrast agent was performed and proved the suspicion of an anomalous aortic origin of the coronary artery (AAOCA) with the left coronary artery arising from the right-facing sinus with an acute take-off angle, a slit-like ostium and an interarterial and intramural course between the aorta and pulmonary artery (**Figure 2**). The further course of the left coronary artery with branching in left anterior descending (LAD) and circumflex artery was normal, as well as the origin and course of the right coronary artery (RCA).

Because of this symptomatic AAOCA with ischemia, there was an indication for a timely operation. Preoperatively, the patient showed no further symptoms, and Troponin T and CK-MB levels declined in the serial laboratory testings. Five days after diagnosis, the patient underwent surgical correction (**Figure 3**). Following installation of the heart-lung machine and cardiologic arrest of the heart, the aorta was opened at the level of the sinotubular junction. The slit-like ostium of the LCA in the right- facing sinus and its intramural course toward the left-facing sinus was identified. Over an inserted coronary probe, the LCA was unroofed with a longitudinal incision into the intima from its ostium up to its off-spring from the aortic root. By this, the ostium was enlarged and the dynamic obstruction of the proximal main stem of the LCA was eliminated. Operation and postoperative course were without complication and the patient recovered quickly. ECG and echocardiography did not show any signs of ischemia and the patient was discharged after 6 days.

In regular follow-ups, the patient is recovering well and has not reported any symptoms of ischemia, at rest or while strenuously exercising. ECG and echocardiography findings remained unremarkable during follow-up on day 30.

Case 2

An otherwise healthy 15-year old girl was admitted with recurring typical and atypical chest pain. She complained of left sided chest pain, especially in the evenings and at night, but also during exercise, which resulted in a reduced physical performance. Her father had died of a sudden cardiac death of unknown underlying cause. In the echocardiography, a coronary artery anomaly of the right coronary artery was suspected (**Figure 4**). The left- and right-ventricular dimensions and functions were normal. Resting ECG and exercise ECG showed no signs of ischemia. When using dobutamine/atropine stress Cardiac Magnetic Resonance (CMR), where a heartrate of 170 bpm was reached, the patient was symptomatic but no wall motion abnormalities were detected with the submaximal hear rate of 83% of the predicted maximum. CCTA confirmed an AAOCA with an origin of the RCA from the left-facing sinus with an interarterial and intramural course between the aorta and the pulmonary artery and a right coronary dominance (**Figure 5**). Because of the symptoms suggesting ischemia and the coronary artery anomaly with anatomic high-risk features, operation with unroofing of the RCA was performed. Unroofing of the RCA was executed in a similar manner to unroofing of the LCA, as explained and illustrated above. In the follow-up, 4 years later, the patient remains symptom free and shows no signs of ischemia in the ECG or echocardiography.

Case 3

An 11-year old girl was admitted to the hospital because of a syncope after swimming. In the medical history, she reported recurring dizziness during exercise in the previous months. Laboratory results showed elevated Troponin T levels. In the initial echocardiography, left ventricular function was reduced to an ejection fraction of 33% with hypokinesia especially of the apex and posterior wall. The patient was hospitalized with suspected myocarditis. On day 4 she developed ventricular fibrillation resulting in cardiopulmonary resuscitation. After return to spontaneous circulation hemodynamic instability persisted, with the need

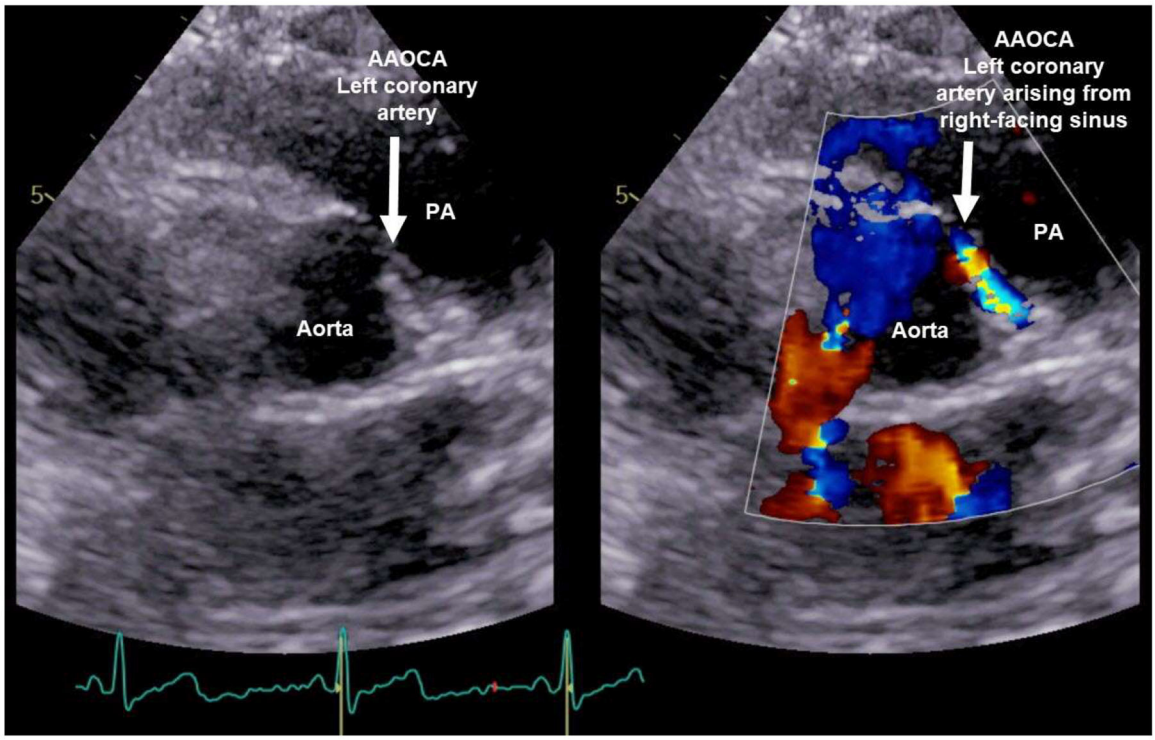

FIGURE 1 | Echocardiography of patient 1: Coronary flow pattern arising from the right-facing sinus and continuing between aorta and pulmonary artery (PA) suggesting an interarterial/intramural course of the left coronary artery.

of extracorporeal membrane oxygenation (ECMO) support. An invasive coronary angiography and an additional CCTA under ECMO showed an AAOCA with an anomalous origin of the left coronary artery arising from the non-facing sinus and the suspicion of a short intramural course of the LCA which may have resulted in coronary ischemia (**Figure 6**). Intraoperatively a long 1 cm segment of an intramural course was confirmed and unroofing was performed. After operation of the LCA, ECMO could be weaned off. Otherwise, the cardiac work-up was unremarkable and initial wall motion abnormalities in the territory of the left coronary artery and the subsequent ventricular fibrillation with heart failure was interpreted due to the prolonged ischemia induced by the coronary artery anomaly. The patient remained symptomatic with congestive heart failure and there was no sign of myocardial recovery over month. Therefore, a biventricular assist device was implanted and she was listed for heart transplantation, which was successfully performed 3 month later.

DISCUSSION

We are reporting on three cases of teenagers, all presenting with an AAOCA and an interarterial and/or intramural course. All three cases showed typical exercise induced symptoms like chest pain, syncope or dizziness. AAOCA is a rare condition with a prevalence of around 1% in the general population (4) and with different variants and relevance, depending on the subsequent course of the anomalous coronary artery. As certain subtypes (those with interarterial/intramural course of the coronary artery) are possibly associated with myocardial ischemia and sudden cardiac death, it is crucial to identify patients at risk, in order to provide optimal care prior to irreversible myocardial damage (1).

This can be difficult as many teenagers with chest pain, syncope and dizziness are seen in pediatric outpatient -and emergency departments. In this age group chest pain is mostly idiopathic or musculoskeletal (5) and also syncope and dizziness are mostly benign in etiology (6). Nevertheless, it is crucial to recognize the red flag associated with exercise induced symptoms (chest pain, dizziness, syncope) in this age group and the need for further diagnostics in these patients.

The thorough work-up, including laboratory testing's, ECG and additional imaging (i.e., echocardiography followed by CMR and/or CT) in order to assess coronary artery anatomy is crucial in this clinical setting to identify the underlying cause. Indeed, only two patients showed elevated Troponin T levels shortly after occurrence of symptoms; in addition, resting ECG and echocardiography can even be misleading, especially because resting ECG does not always show signs of ischemia. Echocardiography can show a broad spectrum from normal function to severely reduced ventricular

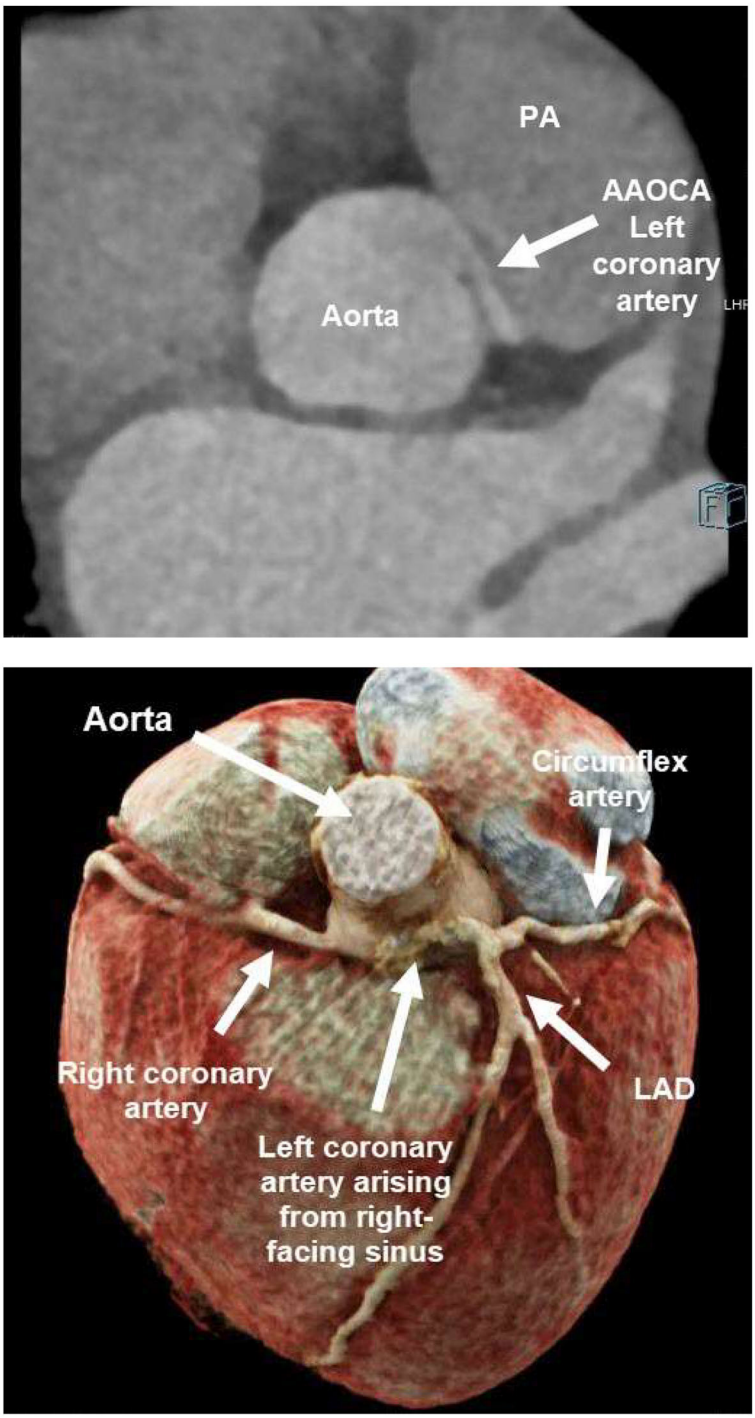

FIGURE 2 | Ultra-low dose coronary computed tomography angiography (CCTA) of patient 1: anomalous aortic origin of the left coronary artery (LCA). LCA arising from the right-facing sinus with acute take-off angle, slit-like ostium and interarterial/intramural course between aorta and pulmonary artery (PA). Normal branching in left anterior descending (LAD) and circumflex artery.

function; the additional problem is, that coronary arteries, especially after the infant period, are often difficult to view in echocardiography. An important and more frequently seen differential diagnosis in teenagers with cardiac symptoms and elevated troponins in combination with and normal or impaired ventricular function, represents acute myocarditis.

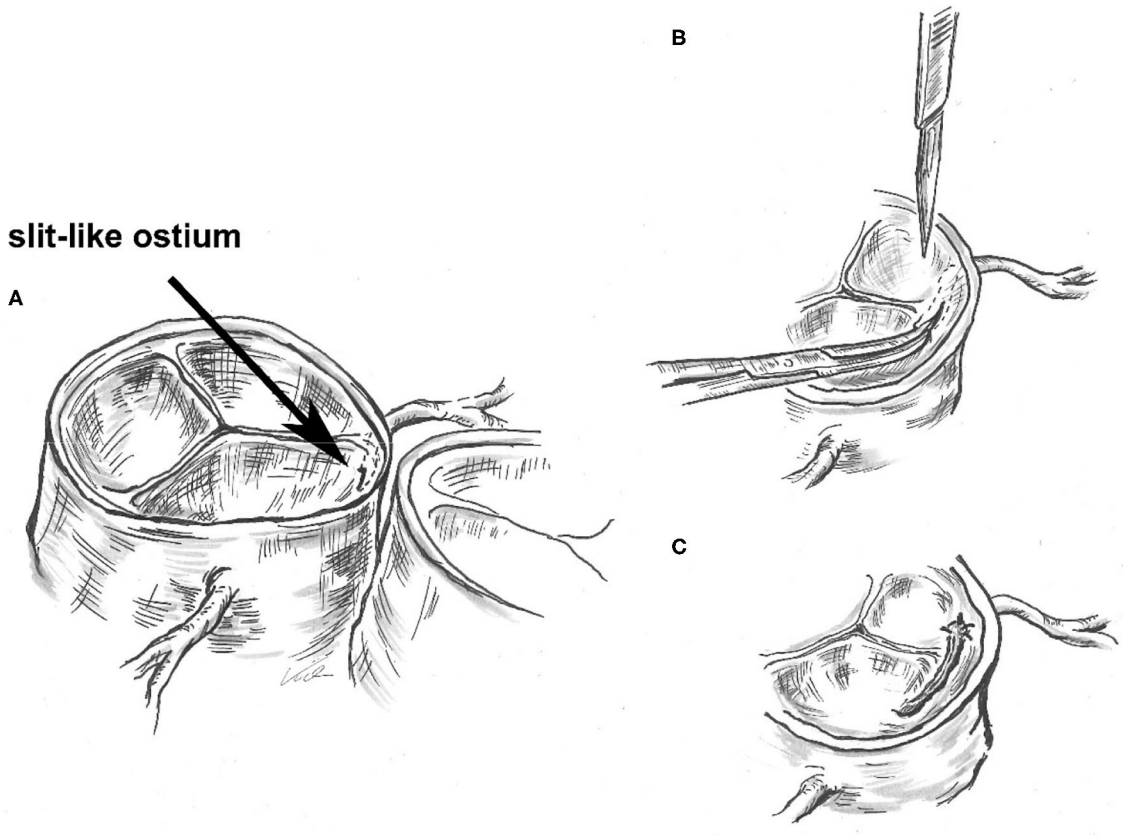

FIGURE 3 | Surgical unroofing of the left coronary artery (LCA): Identification of the slit-like ostium of the LCA in the right- facing sinus and its intramural course toward the left-facing sinus **(A)**. Unroofing of the LCA with a longitudinal incision into the intima from its ostium up to its off-spring from the aortic root **(B)**. By this, enlarging the ostium and eliminating the dynamic obstruction of the proximal main stem of the LCA **(C)**.

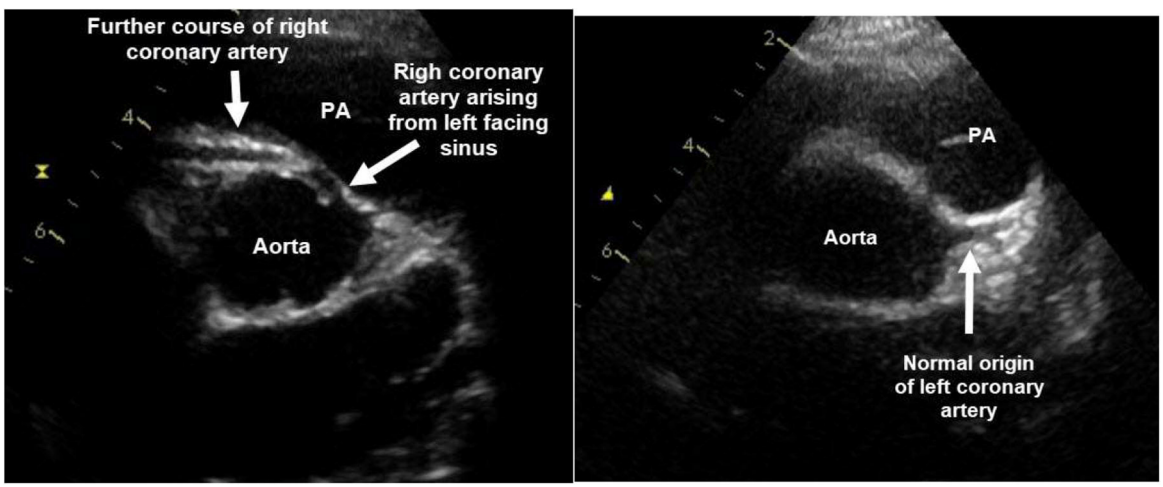

FIGURE 4 | Echocardiography of patient 2: Origin of the right coronary artery (RCA) from the left-facing sinus with an interarterial and intramural course between the aorta and the pulmonary artery (PA). Normal origin of the left coronary artery from the left-facing sinus.

Therefore, if suspected, further imaging is imperatively needed to exclude myocarditis and to clearly depict the coronary artery anatomy and their course. CMR is the ideal tool to diagnose myocarditis and also to depict coronary artery anatomy. CCTA is, depending on the institution, the first line non-invasive imaging modality to depict in high

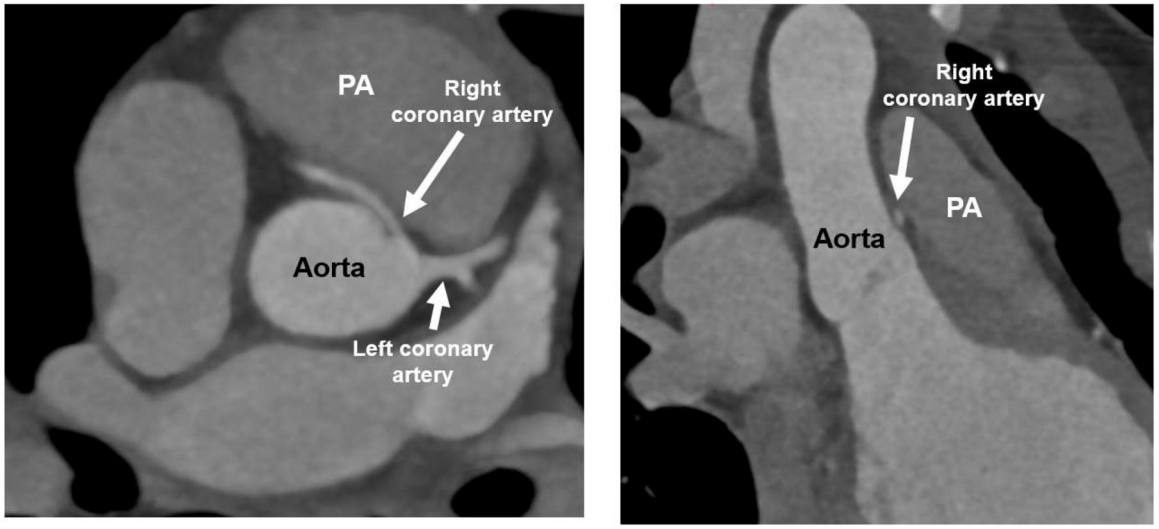

FIGURE 5 | Ultra-low dose coronary computed tomography angiography (CCTA) of patient 2: AAOCA with an origin of the RCA from the left-facing sinus with an interarterial and intramural course between the aorta and the pulmonary artery and a right coronary dominance. PA, pulmonary artery.

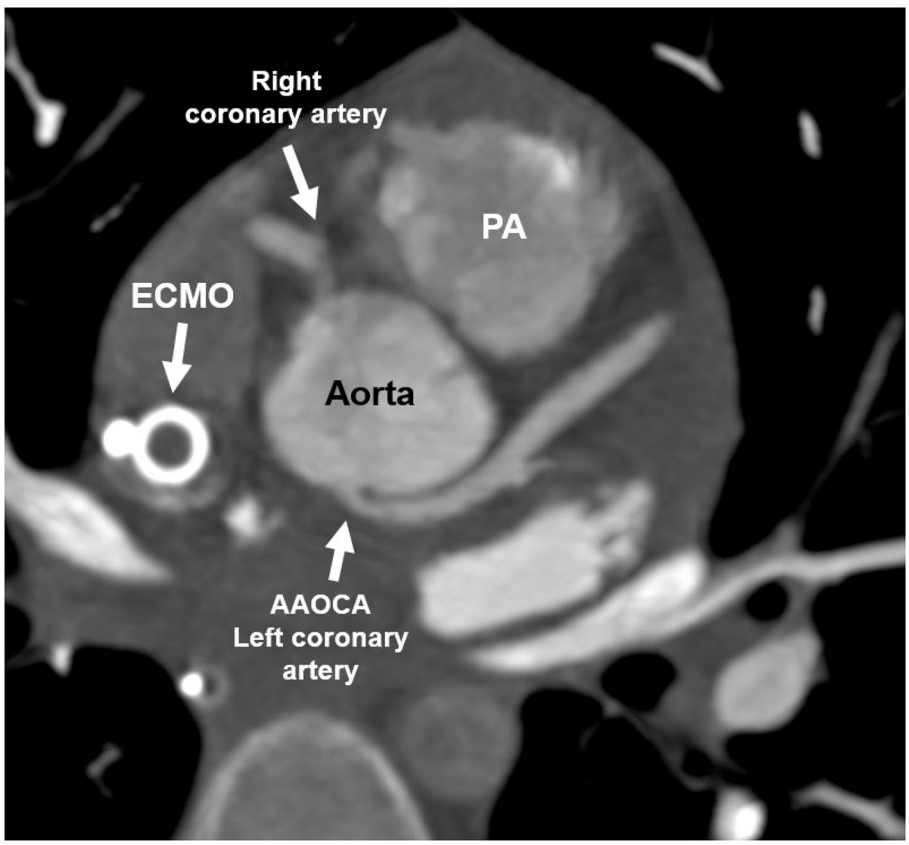

FIGURE 6 | Coronary computed tomography angiography of patient 3: AAOCA with an anomalous origin of the left coronary artery arising from the non-facing sinus without an interarterial course, but with a short intramural course. ECMO, Extracorporeal membrane oxygenation; PA, pulmonary artery.

spatial and temporal resolution the coronary artery anatomy (7). Unroofing is the procedure of choice to correct the intramural segment of AAOCA in young patients. In our case and in accordance to other reports (8), outcome after unroofing is favorable with low risk of surgery and excellent intermediate-term survival.

CONCLUSION

In conclusion, even though infrequent, AAOCA in teenagers is a relevant and potentially life threatening congenital anomaly, which should be diagnosed and treated accordingly.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JB and J-PP drafted the initial manuscript. CG, AK, and MG critically reviewed the manuscript. All authors approved the final manuscript.

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Place of Angioplasty for Coronary Artery Anomalies With Interarterial Course

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Few patients with an anomalous aortic origin of a coronary artery (AAOCA) require a correction of this congenital anomaly. Current recommendations offer surgical repair as a first line therapy to prevent a sudden cardiac death as a main objective. However, these guidelines are focused on children and not based on randomized controlled studies. Furthermore, decision-making should be different in an adult population less exposed to the risk of sudden cardiac death. Current practices showed reluctance to offer a surgical treatment for right AAOCA associated with ischemic symptoms or myocardial ischemia. Our aim in this review is to expose the rationale for percutaneous coronary intervention in right AAOCA with interarterial course and to present the published results.

Keywords: congenital coronary anomaly, anomalous aortic origin, interarterial course, angioplasty, stenting

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INTRODUCTION

Diagnosis of an anomalous aortic origin of a coronary artery (AAOCA) is not rare in the adult population. A prevalence of 0.8% has been reported with coronary computed tomography angiography (CCTA) (1). Only a part of AAOCA (roughly one-third, i.e., anomalies with an interarterial course between the great vessels) may be associated with cardiovascular events or symptoms (2). The first presentation of these anomalies, so-called AAOCA at risk, is variable, ranging from an incident finding to ischemic symptoms or sudden cardiac death (SCD). The latter is rarely the first event in adults >35 years of age (3). Functional tests are often not able to demonstrate inducible ischemia, even in symptomatic patients (4). When an AAOCA correction is offered, surgical intervention is recommended in current guidelines. But the latter are generally focused on young people (5, 6). The optimal management strategy for older patients with AAOCA at risk remains debated given uncertainties related to the individual risk of SCD or aborted sudden cardiac arrest (SCA), corrected-and not corrected AAOCA natural history, and the risks and failures of the surgery (7). Multidisciplinary teams in charge of AAOCA in the adult population are sometimes faced with a difficult therapeutic choice between a conservative strategy and surgery (8). This review aims to present the possibilities offered by percutaneous coronary intervention (PCI) which may be a realistic alternative to surgery. The PCI management of AAOCA associated with a significant coronary artery disease (CAD) will not be addressed in this review. This work describes the experience and point of view of a French team dedicated to the ANOmalous CORonary arteries: the ANOCOR Working Group.

RATIONALE FOR TREATMENT

Several points can be highlighted to understand the rationale for a treatment in the management strategy of AAOCA.

Sudden Cardiac Death

The relationship between AAOCA and SCD has been established a long time ago (9–12). The risk of SCD leads to anxiety for patients with AAOCA identified at risk, and numerous interrogations for referring practitioners. Post-mortem studies showed that AAOCA is one of the most frequent causes of SCD in athletes (13, 14). Unfortunately, we have no tools to stratify the individual risk of SCD in patients with AAOCA. While the absolute risk is only based on estimations (annual risk of 0.2 and 0.02% for left and right coronary artery, respectively), this risk is particularly low in comparison to the risk of other congenital cardiac diseases identified at-risk of SCD (i.e., hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, or electric syndromes) (7, 15, 16). The pathophysiological mechanisms that lead to SCD are not fully understood. Physical effort induced-myocardial ischemia is only one of the factors leading to a fatal ventricular arrhythmia. Age <30 years, intense exercise activities, syncope on exertion, left (L)-AAOCA with interarterial course, and maybe myocardial fibrosis scars, are recognized as risk factors for SCD (3, 4, 16, 17). Unfortunately the majority of L-AAOCA at risk is diagnosed postmortem (18). SCD has been described over 35 years of age, but seems particularly rare, especially in patients with right (R)-AAOCA (3). Therefore, the question of primary prevention of SCD should not be asked in the same way for, on the one hand, a young population with L-AAOCA, and on the other hand, older patients with R-AAOCA. After an aborted SCA, a surgical correction is recommended (19), and an internal cardioverter defibrillator is sometimes discussed.

Ischemic Symptoms and Myocardial Ischemia

A vast majority of AAOCA at risk may remain asymptomatic for a long time, ischemic symptoms, that may mimic a CAD, are possible. AAOCA diagnosis is made by invasive coronary angiography (ICA) or CCTA. Given the difficulty to demonstrate myocardial ischemia by functional non-invasive tests in AAOCA, it seems acceptable to consider non-equivocal symptoms (angina, dyspnea, and syncope, especially on exertion) as ischemic symptoms, even if documented myocardial ischemia is lacking. Symptoms highly suggestive of ischemia are generally included in algorithms for the management of AAOCA (5, 6, 20, 21). Silent myocardial ischemia and severe ventricular arrhythmias must be taken into account in the same way. Considering our knowledge and current guidelines on CAD, medical treatment, PCI, or surgery could be discussed for a symptomatic patient with AAOCA, with the main goals of functional improvement and cardiac events prevention. No controlled randomized study to date has compared the use of anti-ischemic drugs to an alternative strategy in the field of AAOCA. If a SCD may be the first cardiac event, prior ischemic symptoms can be found in nearly half of the cases by questioning the bystanders, entourage or the patient himself in case of aborted SCA (15). Therefore, a correction should always be discussed in AAOCA with ischemic symptoms or documented myocardial ischemia, regardless of age.

Current Recommendations

Surgery is recommended as first line therapy in current guidelines for symptomatic AAOCA with interarterial course. In the expert consensus guidelines from the American Association for Thoracic Surgeons (AATS), the authors give a Class 1/Level B indication for any patient with a L-AAOCA at risk, with or without symptoms, or with a symptomatic R-AAOCA at risk (5). In the 2018 AHA/ACC guidelines for the management of adults with congenital heart disease, surgery is recommended (Class 1, Level B-NR) for AAOCA at risk with ischemic symptoms or myocardial ischemia, and is reasonable (Class IIa/Level C-LD) for L-AAOCA at risk without ischemic symptoms or documented myocardial ischemia (6). Surgery or continued observation may be reasonable (Class IIb/Level B-NR) in asymptomatic R-AAOCA without inducible myocardial ischemia or anatomic severity criteria. AATS guidelines don't offer surgery in R-AAOCA without ischemic symptoms or myocardial ischemia. The recent European Guidelines are very close to the Nord American recommendations (21). While the risk of SCD depends strongly on age, the latter is not always taken into account in the current guidelines. To date, none of these recommendations is based on randomized controlled studies. Some authors have pointed out that we don't have objective evidence to strongly recommend surgery in all circumstances. The place of PCI is only addressed in AATS guidelines (5), for adults with high risk for surgery (Class IIb/Level C).

Strengths and Weaknesses of Surgery

Several surgical techniques have been developed in the field of AAOCA. Because of the risk of competitive flow, coronary artery bypass grafting is not recommended unless it is associated to a proximal coronary ligation, or in patients with significant CAD beyond the interarterial course. A more anatomic approach is to create a neo-orifice in the appropriate sinus, either by an unroofing procedure with ablation of the intramural aortic segment, or by ostioplasty with patch enlargement (22). A direct reimplantation technique is generally not suitable. Surgical anatomic repair permits to bypass an interarterial course associated or not with an intramural segment. Nevertheless, these therapies carry some risks, and the net benefit against the risk of SCD has not yet been clearly proved. The perioperative mortality is remarkably low at almost zero, with a mild morbidity related to complications of sternotomy and extracorporeal circulation (23, 24). Other complications in relation with surgical technique have been described. Aortic insufficiency by injury of the intercoronary commissure is the main complication

Abbreviations: AAOCA, anomalous aortic origin of a coronary artery; AATS, American Association for Thoracic Surgeons; ANOCOR, ANOmalous CORonary arteries; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ICA, invasive coronary artery; IVUS, intravascular ultrasound; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; SCA, sudden cardiac arrest; SCD, sudden cardiac death.

observed after an unroofing procedure (25, 26). Early and late complications have also been described with ostioplasty, such as acute occlusion, scarring stenosis, or pseudo-aneurysm (26). The risk of SCD or myocardial ischemia must be heightened against the risk of surgery and the risk of potential late complications. Rarely, aborted SCA has been reported after surgical repair of AAOCA (26).

ANATOMICAL AND PHYSICAL CONSIDERATIONS

The nature of coronary narrowings related to atherosclerosis or congenital disease differs greatly.

Coronary and Aortic Anatomic Considerations

It is admitted that a slit-like orifice is associated with an intramural aortic pathway. However, all AAOCA with interarterial course are not associated with the latter (27, 28). An intramural pathway implies a direct contact between the coronary media and aortic media. Coronary lumen deformation observed in AAOCA with interarterial course should be interpreted as an adaptation of angiogenesis to the limited space between the great vessels, and not as an extrinsic compression. An eccentric deformation with reduction of the lumen area is generally present in AAOAC with an interarterial course (29). Association of an acute connection angle $<30^{\circ}$ with a ratio >1.5 between long axis and short axis at the narrowest point refers to the presence of an intramural coronary segment embedded within the media of the aorta. The degree of surface reduction varies between 30 and 80%. The length of the interarterial course segment, generally >20 mm, may vary depending of the site of the ectopic orifice. Without intravascular ultrasound (IVUS) guidance, the measurement of the intramural segment length is difficult.

Coronary Physical Considerations

Vascular lumen hypoplasia observed on any interarterial segment could be at least partially corrected by stenting. Our experience in CAD related-PCI showed that a lumen oversizing is possible by stenting of coronary arteries whose wall thickness is <0.5 mm. The intramural aortic pathway is associated with specific anatomic features, such as an ellipsoid section and a particularly thick wall (at least 1.0 mm with two media layers) due to the coronary wall embedded into the aortic wall. As a result, the required forces should be greater to optimize the remodeling of an ellipsoid section with an important increase in the minimal diameter and a small decrease in the maximal diameter. A post-PCI circular shape is probably not an achievable target in case of intramural pathways. Due to the non-circular initial shape, mal-apposition of some struts at the edges may be possible. Risks of elastic recoil remain unknown after stenting of a thick arterial wall free of atherosclerosis. Given the proximity of the great vessels, distortion and/or fracture of metallic stents may be a cause of PCI failure with restenosis after several years of dynamic changes. Early in-stent restenosis by intimal hyperplasia remains possible. Aortic wall dissection during catheterization and balloon inflations can be an additional potential risk of the procedure.

Mechanical Properties of Stents

Uncertainties exist regarding the optimal result of AAOCA stenting. Stents are metallic structures that oppose compressive arterial forces. The mechanical characteristics of stents have not yet been studied in AAOCA. The concept of stenting was developed to improve the results of a balloon dilatation, with a better compression of the atherosclerotic burden and a lesser vascular elastic recoil. Coronary segments with an interarterial course are generally free of atherosclerosis. Basically, the aim of stenting in AAOCA will be performing a vascular remodeling.

GOALS OF PCI

There are anatomic and clinical objectives. Structural rigidity of stents may allow them to correct some anatomic features. Ostioplasty of a slit-like orifice and widening of an arterial segment hypoplasia are the expected effects of coronary stenting in this setting. In addition, metallic stents could prevent the presumed interarterial compression and dynamic changes of the intramural lumen morphology during intensive exercise. Clinical objectives are similar to those of the surgery, but in a different manner. The control of ischemic symptoms and the correction of induced myocardial ischemia should be the main objectives of PCI for the target population to be described further. The prevention of major cardiac events such as SCD is of course also expected.

PCI PLANNING

The next part of this review will be focused on the management of R-AAOCA. Indeed, the vast majority of adults for whom a correction is discussed, has R-AAOCA. Moreover, our current knowledge in the field of AAOCA should encourage us to keep surgery as a first line therapy for L-AAOCA, except for adults with high surgical risk.

Indication of PCI

The evaluation and management of patients with AAOCA at risk should be best discussed by a dedicated multidisciplinary team (cardiologists, radiologists, and surgeons with experience in the AAOCA field). A standardized algorithm, regularly revised, should allow an optimal decision-making for each patient according to the initial presentation and diagnostic work-up. Patients aged over 30 years with R-AAOCA associated with ischemic symptoms and/or documented myocardial ischemia represent the potential population eligible for PCI.

Non-invasive Imaging Evaluation

Adequate imaging is essential to define anatomic characteristics. Currently CCTA is considered as the best tool to delineate accurately the ostium shape and initial morphology of AAOCA in the adult population (1, 30, 31). A standardized interpretation is recommended including ostial morphology, take-off angle,

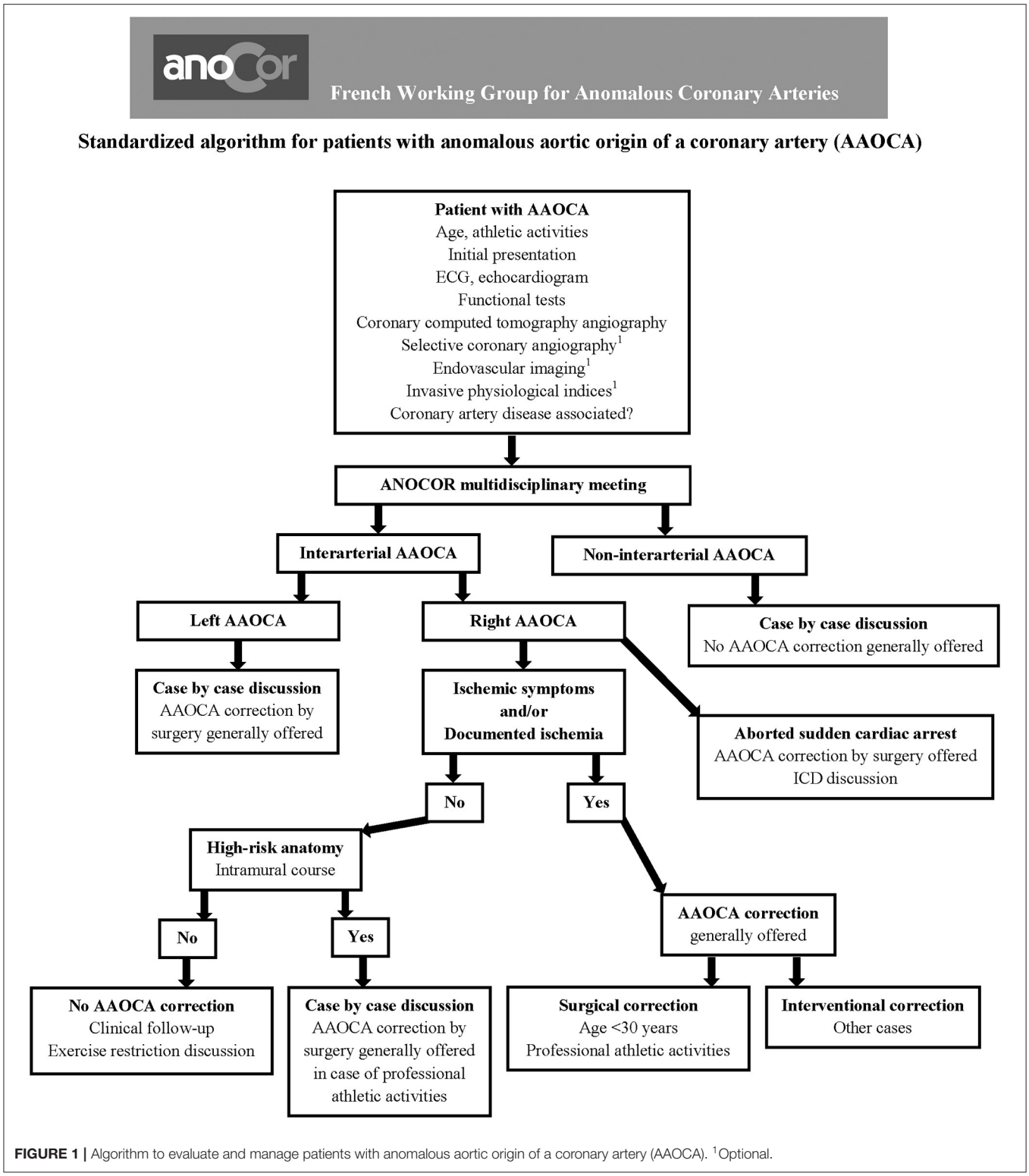

FIGURE 1 | Algorithm to evaluate and manage patients with anomalous aortic origin of a coronary artery (AAOCA). [1]Optional.

degree of proximal narrowing compared to the distal part, degree of proximal lumen eccentricity defined as height/width ratio, presence and length of an intramural pathway, and length of the interarterial course. An interarterial course is easy to recognize by CCTA, but the assertion of an intramural pathway can be difficult.

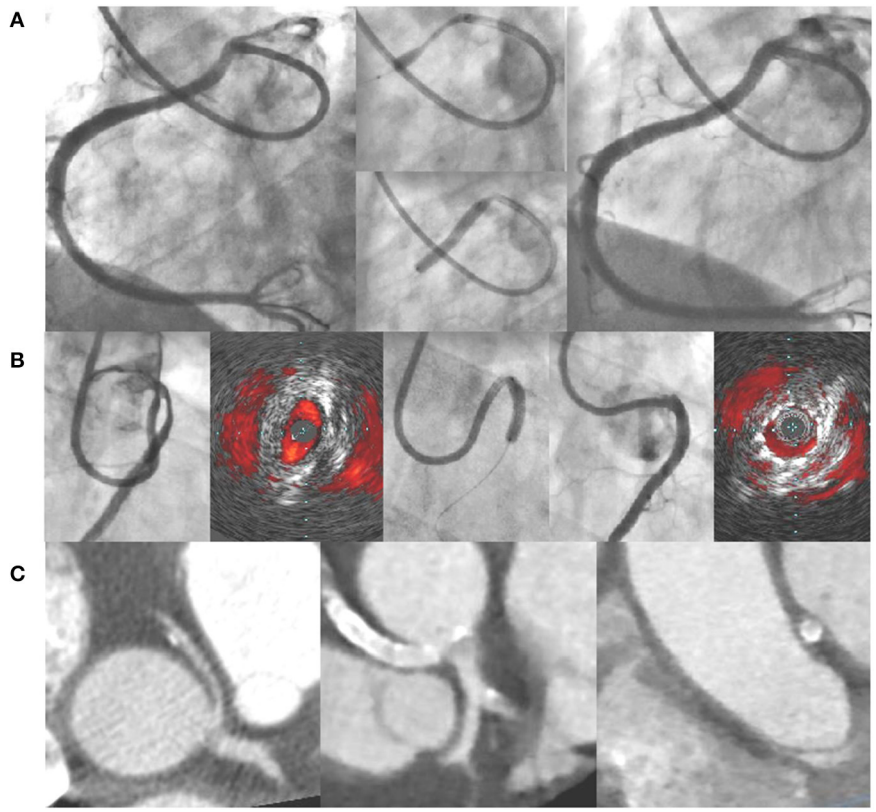

FIGURE 2 | (A) Example of angioplasty with stenting of a right AAOCA (pre-PCI, stent deployment, post-PCI); **(B)** angioplasty with stenting under IVUS guidance of a right AAOCA associated with an intramural pathway (pre-PCI, stent deployment, post-PCI); **(C)** CCTA images of a right AAOCA treated by angioplasty with stenting (pre-PCI and post-PCI at-6 month). AAOCA, anomalous aortic origin of a coronary artery; CCTA, coronary computed tomography angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

TABLE 1 | Main characteristics of patients included in series of AAOCA treated by angioplasty with stenting.

References	AAOCA type and number	Mean age years	BMS/DES number	Angiographic success (%)	Mean follow-up years	In-stent restenosis number (%)	Stent compression number (%)	Sudden cardiac death number
Doorey et al. (33)	3 Left/9 Right	56	12/0	100	0.5	3 (25)	1 (8)	0
Angelini et al. (35)	42 Right	48	3/39	100	5.0	4 (10)	0	0
Degrell et al. (39)	17 Right	51	1/16	100	2.0	2 (12)	0	0
Darki et al. (36)	4 Right	64	0/4	100	8.5	NA	0	0

AAOCA, anomalous aortic origin of a coronary artery; BMS, bare metal stent; DES, drug eluting stent.

Techniques of Catheterization

Technical difficulties with catheters are often experienced with R-AAOCA. Given that the initial course is tangential to the aortic wall, canulation and coaxiality, with adequate back-up support, are frequently challenging. A slit-like orifice does not allow a selective canulation. Amplatz left (AL) type catheters are generally the first choice, but Extra-Back-Up (EBU) type catheters can be used. Subselectively advancing of a coronary guide-wire permits enhanced support and higher quality angiographies.

Invasive Imaging and Physiological Evaluation

Accurate morphological evaluation of AAOCA at risk is crucial. In the 2018 AHA/ACC guideline (6), coronary angiography using catheterization for anatomical and physiological evaluation is recommended in the adult population with AAOCA at risk (Class I, Level C-LD). To date, intravascular ultrasound (IVUS) appears as the imaging technique which provides the best qualitative and quantitative evaluation of the anatomy of AAOCA with an interarterial course (29). IVUS imaging visualizes the aortic

wall at the level of an intramural pathway. The ostial shape and coronary narrowing are easily identified by IVUS with a manual pull-back method. Optical Coherence Tomography (OCT) can be used, but an adequate visualization of the orifice shape can be difficult. Physiological evaluation with pressure flow wires could be interesting. However, the Fractional Flow Reserve (FFR) measurement presents some pitfalls in AAOCA. The lack of selective injection needs a hyperemia induced by intravenous adenosine. In addition, the FFR cut-off for AAOCA is unknown. In a series of 25 R-AAOCA (32), a FFR value $\leq$0.80 was observed in five of the cases (20%). Rest indices such as iFR (instantaneous wave-Free Ratio) remain to be evaluated. So far, we don't have sufficient data to offer a FFR-guided treatment strategy in patients with AAOCA. Nevertheless, a physiological evaluation can be undergone when the decision making is difficult.

Techniques of Angioplasty

Remodeling of the lumen appears to be the main objective of PCI. Direct stenting is recommended. However, some operators proposed a pre angioplasty with a cutting-balloon. Empirically, drug-eluting stents with thicker struts and implanted with high pressures ($\geq$20 bars) should be used. The choice of the stent size should be at least the diameter of the coronary segment just downstream of the ectopic course. The stent should be deployed along the entire ectopic course, avoiding too much protrusion into the aorta. PCI guidance by IVUS is recommended for the evaluation of the ectopic segment (diameters, area, and length) and for the control after stenting.

RESULTS OF PCI

Published Data

The published literature of PCI for AAOCA with an interarterial course remains limited (33–36). Specific treatments of interarterial segment narrowings by PCI should not be confused with percutaneous interventions planned for atherosclerotic stenosis on distal segments of AAOCA with an interarterial course. Several intravascular ultrasound series suggest that the interarterial course of AAOCA is usually free of atherosclerotic disease (32, 37, 38). Doorey et al. reported in 2000 the first experience of PCI for AAOCA with an interarterial course in 12 patients with a mean age of 55 years [44–70] (33). All patients (3 L-AAOCA and 9 R-AAOCA) had abnormal nuclear perfusion imaging tests before stenting. Angiographic success with bare metal stents was obtained in all patients without complications. All patients had normal myocardial functional tests at 6-month follow-up. Angelini et al. have reported in 2015 the largest series with 42 patients with right AAOCA, who underwent PCI because of significant symptoms, positive stress tests, and/or significant stenosis (35). Interestingly, 5 patients had had previous coronary artery bypass grafting to treat R-AAOCA (4 non-functional internal mammary artery grafts and one occluded venous graft). The stenting procedure performed under IVUS guidance was successful in all patients without complications. Drug-eluting stents were used in a majority of cases (39/42). The cross-sectional area increased after stenting from 4.8 to 10.8 mm^2, reducing the stenosis area from 58 to 8%. Twenty-three (55%) patients underwent follow-up test stressing by nuclear perfusion imaging; only two had perfusion defects in the stented areas. During follow-up (mean 5.0 $\pm$ 2.9 years; range 1.1–12.1 years) a significant in-stent restenosis was diagnosed in 4 (10%) patients; two of them had bare metal stents. Three patients underwent in-stent balloon angioplasty and one patient underwent surgery with a mammary artery graft at 6 years for iterative restenosis. Darki et al. reported recently a short series of 4 R-AAOCA treated with drug-eluting stents (36). All patients were symptomatic at presentation. Angiographic success was achieved in all of the cases. All patients were symptom-free after PCI. On the follow-up CCTA (mean duration of 1.4 years), no evidence of stent distortion or fracture was observed. Furthermore, PCI can be used to treat some surgery failures, such as acute occlusion or scarring stenosis (26).

ANOCOR Working Group Experience

Based on this experience reported in the literature, the ANOCOR Working Group has started since 2014 a prospective registry (ANOCOR Stenting) of patients with R-AAOCA and treated by PCI with stenting (39). All patients were discussed in monthly multidisciplinary meetings. A decision-making algorithm (**Figure 1**) was applied for the evaluation and management of patients with AAOCA. Aborted SCA was considered an exclusion criteria. A percutaneous treatment by stenting was proposed for patients with R-AAOCA referred to the expert group according to predefined criteria: age >30 years (except for patients with a left coronary dominance), ischemic symptoms or documented myocardial ischemia, interarterial course). All patients underwent invasive CA and CCTA. Additional evaluation by IVUS or OCT was recommended. Clinical follow-up was scheduled at 6, 12, and 60 months by phone contact. Systematic CCTA and functional testing with imaging were proposed between 6 and 12 months. Patients continued dual antiplatelet therapy for at least 6 months. Seventeen patients (mean age 51 years) were prospectively included between 2014 and 2019. Two patients had acute coronary syndrome, twelve had stable angina, two were asymptomatic with a positive stress test and one had syncope. An intramural segment was identified in more than half of the patients. Stenting was successful with residual angiographic stenosis <30% in all of the procedures, 47% radial access, 94% of drug-eluting stents, mean stent diameter 3.5 mm, mean stent length 25 mm, mean fluoroscopic time of 19 min, and >80% of IVUS or OCT guidance. Coronary morphology is modified by stenting with a trend toward a more circular lumen (**Figure 2**). However, the latter remains generally ovoid after stenting of an intramural pathway. There were no periprocedural complications. Clinical follow-up at 6 months was uneventful in all but one patient requiring a new hospitalization at 5 months for persistent angina reported to be a vasospastic angina. Two patients had in-stent restenosis between 6 and 12 months post-procedure needing a new PCI. No stent distortion was observed on follow-up CCTA (**Figure 2**).

LIMITATIONS AND STRENGTHS OF PCI

As the surgery, we don't know the long-term outcomes of the management of AAOCA with PCI (**Table 1**). The strengths of the latter in comparison with the surgery are those usually observed in the CAD treatment, with a shorter hospital stay and less post procedural adverse events with the percutaneous approach. In addition, the latter may be accomplished by the vast majority of interventional cardiologists. In opposite, few cardiac surgeons are able to repair AAOCA.

DISCUSSION

R-AAOCA constitutes a major part of congenital coronary anomalies possibly responsible for ischemic symptoms or myocardial ischemia. The management of patients with R-AAOCA remains controversial in the adult population. Current guidelines recommend a surgical repair for R-AAOCA with evidence of ischemia. A very low risk of SCD, the lack of randomized controlled studies and scarcity of long-term data may explain the low rate of surgically treated patients. A percutaneous approach may provide an interesting alternative in a selected adult population. Our experience and that of others showed that stenting of an interarterial course was feasible and safe without risks of aortic or coronary dissection. Arterial remodeling associated with a significant increase in lumen area can explain symptom relief and myocardial ischemia resolution. The design of the abovementioned studies did not allow the evaluation of the impact of stenting on SCD risks. We should consider the risk of in-stent restenosis (about 10% of cases) that can be difficult to treat in case of strut protruding into the aorta. An extrinsic compression of a metallic stent placed between the great vessels has not been reported yet. More information is needed with longitudinal studies of a larger population, longer clinical and CCTA follow-ups, and prospective data collection. In the future, a percutaneous option for the treatment of selected R-AAOCA should be considered in the decision-making algorithm in specialized centers.

AUTHOR CONTRIBUTIONS

PA wrote the initial draft of the review and supervised corrections. PD contributed substantially to the content of the review. XHF and OB reviewed all drafts, providing revisions. All authors agree to be accountable for the content of the work.

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REVIEW
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Hemodynamic Relevance of Anomalous Coronary Arteries Originating From the Opposite Sinus of Valsalva-In Search of the Evidence

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Coronary artery anomalies (CAA) represent a heterogeneous group of congenital disorders of the arterial coronary circulation, defined by an anomalous origin of the coronary ostium and/or vessel course. Of particular interest are anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS). The interarterial variants (with the anomalous vessel situated between the great arteries) are historically called "malignant," based on an anticipated higher risk for myocardial ischemia and sudden cardiac death (SCD), especially affecting young patients during strenuous physical activity. However, the interarterial course itself may not be the predominant cause of ischemia, but rather represents a surrogate for other ischemia-associated anatomical high-risk features. As the exact pathophysiology of ACAOS is not well-understood, there is a lack of evidence-based guidelines addressing optimal diagnostic work-up, downstream testing, sports counseling, and therapeutic options in patients with ACAOS. Therefore, treating physicians are often left with uncertainty regarding the clinical management of affected patients. This review focuses on the pathophysiologic consequences of ACAOS on myocardial ischemia and discusses the concept of the interplay between fixed and dynamic coronary stenosis. Further, we discuss the advantages and limitations of the different diagnostic modalities and give an outlook by highlighting the gaps of knowledge in the assessment of such anomalies.

Keywords: anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS), multimodality imaging, hemodynamic relevance, fixed vs. dynamic stenosis, anomalous aortic origin of the coronary artery (AAOCA), dobutamine-volume challenge, fractional flow reserve (FFR), intravascular ultrasound (IVUS)

INTRODUCTION

Coronary artery anomalies (CAA) represent a heterogeneous group of congenital disorders of the arterial coronary circulation, hallmarked by the anomalous origin of the coronary ostium, vessel course, and/or unusual number (1). CAAs are the consequence of an anomalous ingrowth from the initially preformed subepicardial vascular plexus into the aortic root during the embryonic period

(2, 3). Reflecting this heterogeneity, clinical presentation varies ranging from normal variants [e.g., myocardial bridges, separate origin of the left anterior descending and circumflex artery (4)], which remains often undetected, to potentially life-threatening anomalies (e.g., ectopic origin of a coronary artery from the pulmonary artery). Of particular interest are anomalous coronary arteries with the origin of the anomalous vessel from the opposite sinus of Valsalva (ACAOS), especially if they follow an interarterial course between the great arteries (i.e., aorta and pulmonary artery). This rare congenital abnormality has a prevalence of 0.26% in the general population (0.03% for left coronary ACAOS; L-ACAOS, 0.23% for right coronary ACAOS; R-ACAOS) (5, 6). These interarterial variants are historically referred to as "malignant" based on the anticipated higher risk for myocardial ischemia and sudden cardiac death (SCD), especially affecting young adults during strenuous physical activity (7–11). Indeed, autopsy series showed that ACAOS were in up to one-third the underlying cause of sports-related SCD in young military recruits in the United States (L-ACAOS more frequently than R-ACAOS) (9, 12, 13). However, this proportion does not reflect the absolute risk of SCD in people *living* with ACAOS (14) that remains very low (15). Furthermore, the interarterial course itself may not be the predominant cause of ischemia, but rather represents a surrogate for other ischemia-associated anatomical high-risk features. Nevertheless, the few available professional guidelines recommend strict sports abstinence in patients with interarterial courses (AHA/ACC 2015, Class IIIB/C, ESC 2020 IIIC) and a low threshold for surgical coronary revascularization (ACC/AHA 2008, Class IB/IIa C, AHA/ACC 2015, Class IB, AHA/ACC 2018, Class IB/IIa C, ESC 2020 IC/IIa C) (16–20). There, surgical revascularization demonstrates favorable outcomes, although long-term implication remains unknown (21). As the level of evidence supporting the guidelines about optimal diagnostic work-up, downstream testing, sports counseling, and therapeutic options in patients with ACAOS is limited, treating physicians are often uncertain how they should counsel their patients (22).

Beside young athletes, substantial interest has emerged for the management of older patients with newly diagnosed ACAOS. This is of particular interest, as with the growing use of non-invasive imaging for the evaluation of coronary artery disease (CAD), the number of newly detected ACAOS is growing. Management strategies in the middle-aged and elderly group is even less well-established compared to young individuals, and range from strict sports restriction and/or revascularization to watchful waiting (14, 16–18, 23) (see **Table 1** for a summary of available recommendations). The latter strategy (i.e., watchful waiting) is supported by growing evidence for possibly decreasing hemodynamic relevance of the ACAOS above a certain age (24), when symptomatic CAD becomes more prevalent (25). Still, whether older individuals might suffer from a lower ACAOS-related ischemic risk compared to younger individuals (25, 26) remains under debate. Furthermore, as the exact pathophysiology is not completely understood, functional imaging methods routinely used for CAD-evaluation are possibly not directly applicable to rule out ACAOS related hemodynamic relevance.

In this review, we will focus on the pathophysiologic consequences of ACAOS on myocardial ischemia. In addition, we will discuss the concept of the interplay of fixed and dynamic stenosis in ACAOS, which is important toward optimal stress test modality selection. Finally, we will discuss advantages and limitations of the different diagnostic modalities and provide an outlook by highlighting the gaps of knowledge in the evaluation of ACAOS patients.

METHODS

The initial literature research started systematically on Medline Ovid and Pubmed with focus on peer-reviewed, English publication on coronary anomalies, diagnostic modalities, and myocardial ischemia within the last 20 years (i.e., 2000–2020). This resulted in 588, respectively, 518 articles, which we further decreased to 201 full text analysis. These were initially included and read by MRB and/or AA. However, as old autoptic studies as well as echocardiography papers were missing, we manually search for the most referenced papers within this topic. Thus, the presented review is methodological narrative.

PATHOMECHANISMS OF ISCHEMIA IN ACAOS

Although there have been several attempts to uncover the pathophysiology of ACAOS during the previous decades, the underlying mechanisms of ischemia remain ambiguous. Historically, the interarterial course was thought to be the crucial abnormality assuming a scissor-like mechanism created by the close proximity of the aorta and pulmonary artery, especially during exertion (7). Considering the pressure condition in the respective circulatory systems, it is unlikely that the low-pressure pulmonary artery would develop substantial counterforce to occlude the anomalous coronary artery. Furthermore, at the site of closest aortopulmonary proximity, the anomalous segment usually runs inside the aortic wall (8, 27, 28). Therefore, the interarterial course may act only as a surrogate for other anatomical high-risk features like slit-like ostium, acute take-off angle, proximal narrowing (also referred to as hypoplasia) with elliptic vessel shape and intramural course (i.e., course within the tunica media of the aortic wall in; see **Figure 1**) (1, 24, 28, 31–39). Consequently, terminology should focus on these features rather than the interarterial course. Beside these anatomic features supported by a large body of evidence, other postulated mechanisms are dynamic lateral compression of the intramural segment (7, 27), flap-like closure of the narrowed ostium (24, 40), and increased vulnerability to coronary spasm (41). However, coronary spasms are rarely observed in clinical practice, unless catheter cannulation inadvertently results in trauma (41, 42). Especially in ACAOS with intramural course, coronary spasm appears implausible because of the embedment of the ACAOS within the aortic tunica media, a layer of elastic tissue without functional smooth muscle cells (43). In addition, provocative testing for coronary spasm using ergonovine elicits no spasticity of the ectopic segment suggesting that spasm is

TABLE 1 | Guideline recommendations regarding diagnostic evaluation and treatment in patients with ACAOS.

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease	AHA/ACC 2018 guidelines for the management of adults with congenital heart disease	2016 AATS expert consensus guidelines: anomalous coronary artery	2015 AHA/ACC scientific statement for competitive athletes with cardiovascular abnormalities	2020 ESC guidelines for the management of adult congenital heart disease	2020 ESC guidelines on sports cardiology and exercise in patients with cardio-vascular disease
The evaluation of individuals who have survived unexplained aborted sudden cardiac death or with unexplained life-threatening arrhythmia, coronary ischemic symptoms, or LV dysfunction should include assessment of coronary artery origins and course. (I B)	Coronary angiography, using ICA, CCTA, or CMR, is recommended for evaluation of ACAOS (I C)	Individuals with suspected ACAOS should undergo TTE to identify the origin and course of the proximal coronary arteries. (I B)	Athletes with R-ACAOS should be evaluated by an exercise stress test. For those without either symptoms or a positive exercise stress test, permission to compete can be considered after adequate counseling of the athlete, taking into consideration the uncertainty of a negative stress test (IIa C)	Non-pharmacological functional imaging (e.g., nuclear study, echocardiography, or CMR with physical stress) is recommended in patients with coronary anomalies to confirm/exclude myocardial ischemia (I C)	When considering sports activities, evaluation with imaging tests to identify high-risk patterns and an exercise stress test to check for ischaemia should be considered in individuals with ACAOS. (IIa C)
CT or CMR angiography is useful as the initial screening method in centers with expertise in such imaging (I B)	Anatomic and physiological evaluation should be performed in patients with ACAOS (I C)	Additional imaging studies, such as CCTA or CMR are reasonable to better visualize the coronary artery anatomy and to confirm the diagnosis. (IIa B)	Athletes with an L-ACAOS should be restricted from participation in all competitive sports before surgical repair (independent from symptoms) (III B)	Surgery is recommended for ACAOS in patients with typical angina symptoms who present with evidence of stress-induced myocardial ischemia in a matching territory or high-risk anatomy (I C)	In asymptomatic individuals with a CAA without anatomical high-risk features, competition may be considered, after adequate counseling on the risks, provided there is absence of inducible ischaemia. (IIb C)
Surgical coronary revascularization should be performed in patients with L-ACAOS with/without documented ischemia R-ACAOS with documented ischemia (I B)	Surgery is recommended for ACAOS (L-and R) for symptoms or diagnostic evidence consistent with coronary ischemia attributable to the ACAOS (I B)	In asymptomatic patients without a history of aborted SCD, exercise stress testing combined with nuclear perfusion scan or echocardiographic imaging should be used to assess the potential ischemic burden of ACAOS (I B)	Non-operated athletes with a R-ACAOS who exhibit symptoms, arrhythmias, or signs of ischemia on exercise stress test should be restricted from participation in all competitive sports (III C)	Surgery should be considered in asymptomatic patients with ACAOS and evidence of myocardial ischemia (IIa C)	After surgical repair of an ACAOS, participation in all sports may be considered, at the earliest 3 months after surgery, if they are asymptomatic and there is no evidence of inducible myocardial ischaemia or complex cardiac arrhythmias during maximal exercise stress test. (IIb C)
Surgical coronary revascularization can be beneficial in the setting of documented vascular wall hypoplasia, coronary compression, or documented obstruction to coronary flow, regardless of inability to document coronary ischemia (IIa C)	Surgery is reasonable for L-ACAOS in the absence of symptoms or ischemia (IIa C)	ICA should be performed in suspected ACAOS if the anatomy cannot be defined with non-invasive imaging, and in adults with risk factors for coexistent atherosclerotic CAD (I B)		Surgery should be considered in asymptomatic patients with L-ACAOS and no evidence of myocardial ischemia but a high-risk anatomy (IIa C)	Participation in most competitive sports with a moderate and high cardiovascular demand among individuals with AOCA with an acutely angled take-off or an anomalous course between the large vessels is not recommended. (III C)
Delineation of potential mechanisms of flow restriction via IVUS can be beneficial in patients with ACAOS (IIa C)	Surgery for ACAOS is reasonable in the setting of ventricular arrhythmias (IIa C)			Surgery may be considered for symptomatic patients with ACAOS even if there is no evidence of myocardial ischemia or high-risk anatomy (IIb C)	

(Continued)

TABLE 1 | Continued

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease	AHA/ACC 2018 guidelines for the management of adults with congenital heart disease	2016 AATS expert consensus guidelines: anomalous coronary artery	2015 AHA/ACC scientific statement for competitive athletes with cardiovascular abnormalities	2020 ESC guidelines for the management of adult congenital heart disease	2020 ESC guidelines on sports cardiology and exercise in patients with cardio-vascular disease
	Surgery or continued observation may be reasonable for asymptomatic patients with ACAOS without ischemia or anatomic or physiologic evaluation suggesting potential for compromise of coronary perfusion (IIb B)			Surgery may be considered for asymptomatic patients with L-ACAOS without myocardial ischemia or high-risk anatomy when thy present at young age (<35 years) (IIb C)	

ACAOS, anomalous coronary arteries with the origin of the anomalous vessel from the opposite sinus of Valsalva; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; IVUS, intravascular ultrasound; SCD, sudden cardiac death.

not contributing to ischemia in ACAOS (27, 44). Similarly, the flap-like closure mechanism is not observed in clinical practice and has only been reported in autoptic studies (24, 40). The failure of demonstrating these mechanisms *in vivo* may be due to the dynamic nature of the phenomenon, which may be missed by imaging. Alternatively, reproducibility may be limited owing to technical issues [e.g., inadequate spatial resolution of non-invasive imaging or blockade of the flap by the intravascular ultrasound (IVUS) or optical coherence tomography (OCT) probe during invasive assessment].

The anatomic high-risk feature of a slit-like ostium at the ectopic origin is defined as a $\geq$50% reduction of the minimal lumen diameter compared to the normal distal reference diameter (36) [<50% = oval ostium (36)] and best corresponds to the concept of relevant coronary stenosis known from CAD. Thus, the deformed coronary ostium with a decreased cross-sectional area acts as an ostial stenosis. In a small study, Kaushal et al. compared the mean ostial diameter of anomalous coronaries to those of normal vessels in 27 young patients undergoing surgical correction of ACAOS and found a significant caliber difference (mean diameter 1.5 $\pm$ 0.4 mm vs. 3.3 $\pm$ 0.8 mm) (45). Accordingly, narrowing of the proximal segment reduces the cross-sectional area in the interarterial part, the relevance of which can be measured using percent diameter stenosis of the anomalous in relation to the unobstructed, distal segment [i.e., (reference area—stenosis area)/reference area*100] (46, 47). In case of a stenosis above 50%, revascularization of the proximal vessel may be considered in symptomatic older patients with R-ACAOS (46, 48). Of note and similar to atherosclerotic lesions, not only percent diameter stenosis but also its length affects the hemodynamic relevance directly.

An acute take-off angle (below 45°), defined as an axial course of the proximal segment tangential to the great vessel circumference (40, 49), was previously associated with symptoms (36, 47). Furthermore, kinking of the anomalous coronary artery during exercise, i.e., decrease of the acute take-off angle and consequently increased narrowing at the ostium, was proposed as a contributing ischemia-inducing mechanism (38, 50).

Finally, the intramural course is probably the most threatening feature in terms of hemodynamic relevance (10, 51). As shown by several studies, the length of the intramural segment is associated with an increased risk for ischemia (28, 36, 45, 52). In addition, an elliptic proximal vessel shape [defined as height/width ratio of >1.3 (53)] is frequent within the intramural segment, and the deformation [also called lateral compression, dependent from the cardiac phase, i.e., more pronounced during systole than diastole (54)] has been shown to increase during physical activity with augmented great vessel wall stress (27, 54–59). Taken into account the law of LaPlace [wall stress = (transmural pressure * radius)/(2 * wall thickness)], the augmented wall stress affects in particular the intramural segment, where there is a substantial decrease in aortic wall thickness. The latter phenomenon is additionally exacerbated by the increasing artery diameter during physical exercise, thereby producing a lateral compression sufficient to cause myocardial ischemia even during diastole. This anatomic feature is not only relevant due to the reduced cross-sectional area compared with a

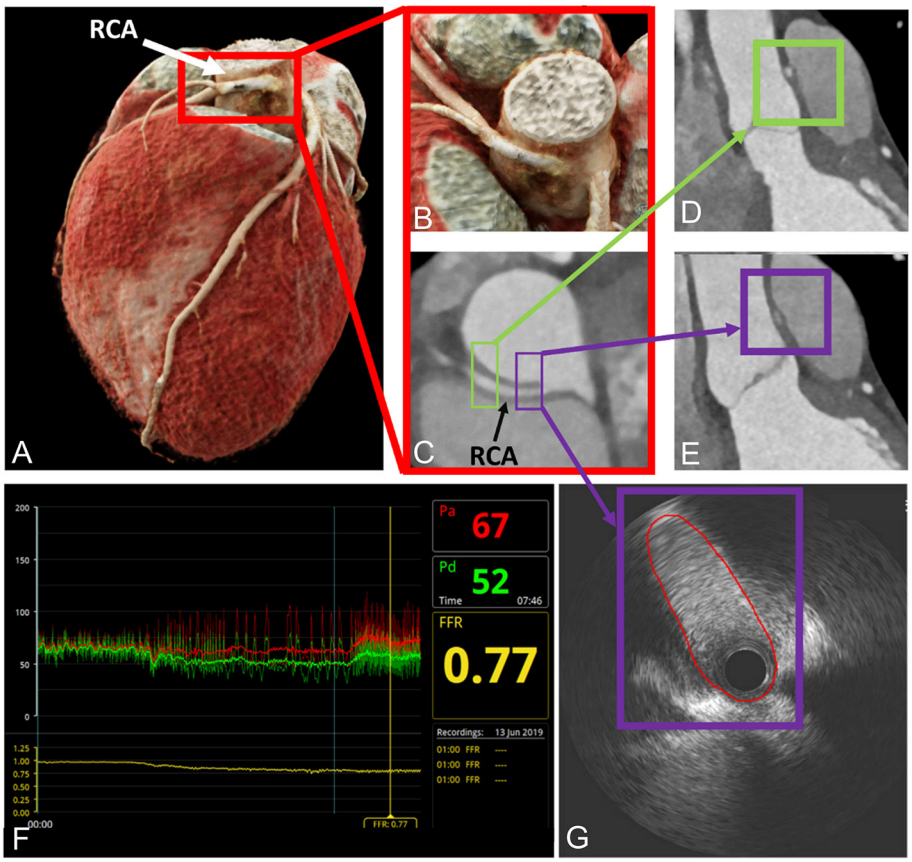

FIGURE 1 | Depiction of anatomical high-risk features in a patient with right ACAOS by coronary computed tomography angiography and invasive coronary angiography. **(A–C)** Illustration of the interarterial course by CCTA; **(D,E)** depiction of anatomical high-risk features [acute-take off-angle, proximal narrowing and oval vessel shape; purple box proximal segment, also called Angelini/Cheong sign (29), green box distal segment]; **(F,G)** invasive assessment with a positive FFR and demonstration of lateral compression by intravascular ultrasound. Red line depicts lumen contour. With permission from Elsevier. Bigler et al. (30).

round vessel shape, but also due to higher resistance as shown by the underlying mechanics, i.e., the law of Hagen-Poiseuille (60). **Figure 2** demonstrates the decreasing cross-sectional area and the increasing resistance, respectively, as a function of the height/width ratio in a vessel with a given circumference. Furthermore, as outlined by the position as a denominator in the applied law, intramural length directly increases resistance to flow as well (60). **Figure 2** is a theoretical model of the effect of vessel deformation with the limitation that deformation will rarely result in a perfect elliptic shape. Nonetheless, it demonstrates the increasing resistance along the anomalous segment during progressive deformation (which would be even higher with irregular deformation and consecutive turbulent flow) and the need for compensatory coronary vasodilatation for the preservation of adequate perfusion at the expense of decreased coronary flow reserve (CFR). This effect was illustrated in a case report by Brandt et al., where the authors measured CFR during surgical revascularization and demonstrated a decreased CFR when the periphery was supplied by the native vessel compared to the graft (44).

Two-Tier Concept

Combining the features outlined above, we support a two-tier concept for the pathomechanisms of ischemia in ACAOS (41). In this concept, the occurrence of ischemia is based on the extent of a fixed (anatomic high-risk features of slit-like ostium and proximal narrowing) and a dynamic (acute take-off angle, intramural course with the elliptic vessel shape) component. In previous studies, none of the anatomic features taken separately correlated with ischemia, indicating a complex interplay between the different components (38, 54). In addition, the hemodynamic relevance depends directly on the supplied viable myocardial mass downstream of the stenosis. Thus, providing an explication for the diverging prognosis of R- and L-ACAOS (9).

Last, ischemia is unlikely to occur every time the patient exercises (61), which suggests the presence of additional factors, e.g., volume status and type of physical activity [isotonic, e.g., cycling or running vs. isometric, e.g., weight-lifting (62, 63)]. Although more SCDs are known in patients participating in dynamic sports, the relevance of this differentiation has yet to be determined.

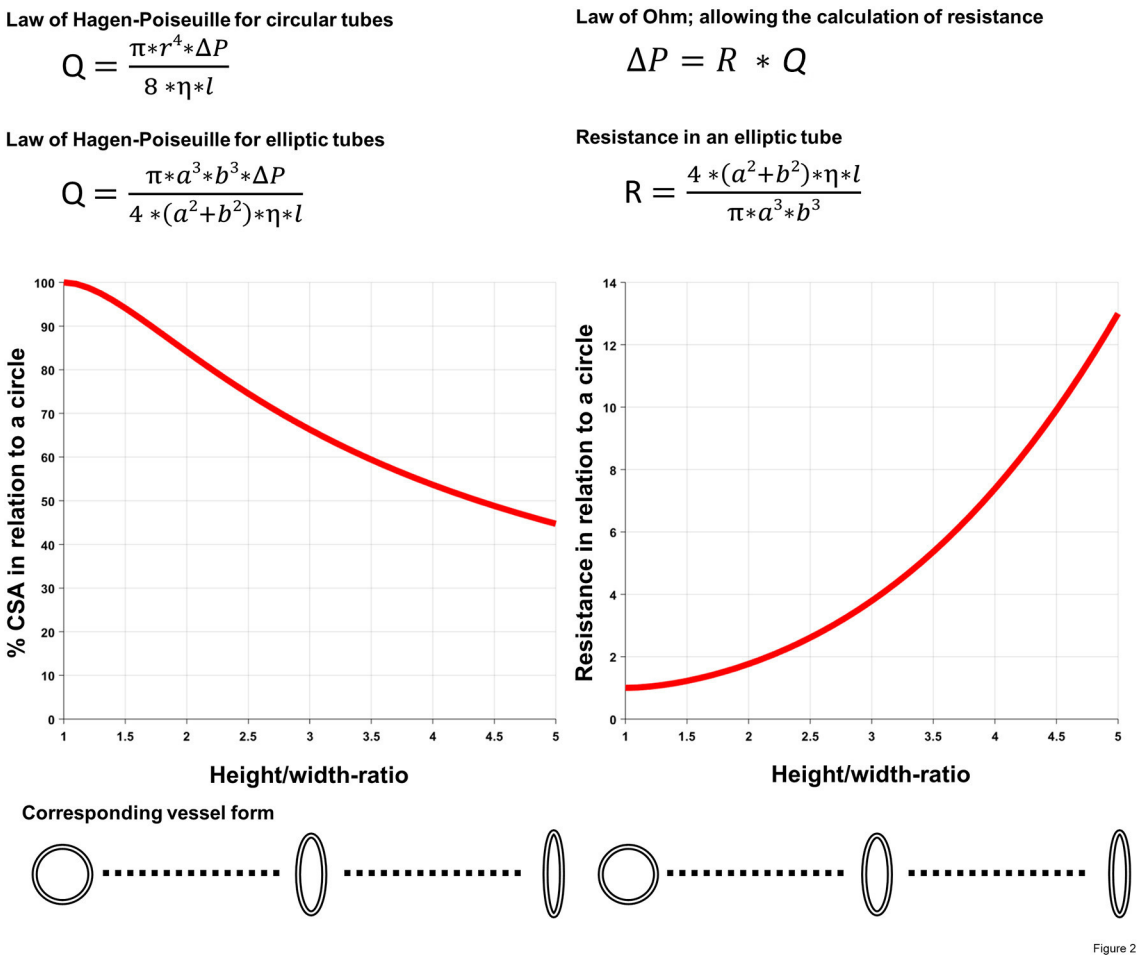

FIGURE 2 | Illustration of the impact of deformed vascular shape (i.e., lateral compression). Using two basic equations of fluid dynamics (law of Hagen-Poiseuille and law of Ohm) as well as common geometric formulas for the calculation of the cross-sectional area (CSA) in different forms, decreasing cross-sectional area, respectively, the increasing resistance as a function of the height/width ratio (i.e., a/b-ratio) in a vessel with a given (i.e., fixed) circumference was calculated. Q, volumetric flow rate; r, radius of the pipe; ΔP, pressure gradient; η, dynamic viscosity; l, length of the pipe; a, short semi-axis of the elliptic pipe, b, long semi-axis of the elliptic pipe; R, resistance; Equations of fluid dynamics taken from (60).

Fixed Component

As discussed above, slit-like ostium and proximal narrowing are present at rest and behave in a similar manner to classic coronary lesions. The reduction of the cross-sectional area creates flow restrictions, which can be evaluated by coronary angiography or intravascular imaging (64) and/or the pressure gradient over the stenotic segment (65). Fractional flow reserve [FFR, defined as the hyperemic mean distal coronary artery pressure divided by the simultaneous recorded mean aortic pressure (65)] with hyperemia induced by pharmacological vasodilatation (i.e., adenosine) was used to assess the hemodynamic relevance of ACAOS in multiple studies (56, 66, 67). Interestingly, only a poor correlation with symptoms and/or anatomic features could be documented (66). In fact, these studies assessed the fixed component alone and thus, found no hemodynamically relevant FFR according to the used threshold for atherosclerotic lesions of 0.80 (68). These findings are consistent with the postulated pathophysiology and explained by the fact that the dynamic component cannot be sufficiently reproduced using pharmacological stress with vasodilators.

Dynamic Component

Anatomic features like acute take-off angle or lateral compression in the intramural segment gain hemodynamic relevance during exercise. With increased heart rate, systolic blood pressure and myocardial contractility, systolic expansion and higher wall stress of the proximal aorta can be observed because of increased dP/dt and stroke volume (69). Thus, lateral compression of the intramural segment and subsequent flow resistance increase as a function of cardiac output and systolic blood pressure, affecting CFR during conditions of increased myocardial oxygen demand. This phenomenon causes myocardial ischemia that cannot be triggered by vasodilatatory drugs. Hence, assessment of the hemodynamic relevance of

ACAOS should be performed preferably using physical exercise or dobutamine, a beta2-sympatomimetica that increases heart rate and stroke volume (46, 54, 56). In a study by Angelini et al. (46), intravascular ultrasound (IVUS) during dobutamine infusion directly demonstrated increased lateral compression. Furthermore, Lee et al. (56) conducted a study in 37 patients, where $FFR_{Dobutamine}$ was performed in case of a negative $FFR_{Adenosine}$ showing discrepancies in three patients, as evidence for a dynamic component of ischemia. Of note, in multiple studies, $FFR_{Dobutamine}$ was usually lower or equal to $FFR_{Adenosine}$, revealing the inconstant presence of the dynamic component (56, 67). It is conceivable, that with increasing age, thickening and stiffness of the aortic wall decrease distensibility (69) and thus, the dynamic component loses its relevance. These findings are in line with the autoptic studies by Taylor et al. (24, 38), which reported a decreased risk for SCD beyond the age of 30. However, the simultaneously increasing risk for concomitant CAD may incur myocardial ischemia owing to the development of atherosclerotic lesions (34), which rarely directly affects the anomalous segment (56, 58, 59). However, both factors may potentiate themselves and result in myocardial ischemia.

Besides anatomic high-risk features and concomitant CAD, a recent study demonstrated the hemodynamic relevance of a so far "benign" ACAOS variant with intraseptal course. There, up to 50% of these anomalies showed inducible myocardial hypoperfusion during non-invasive stress testing, which was later confirmed by positive invasive FFR (70). Hence, repeated in-depth hemodynamic evaluation with up-to-date non-invasive and invasive testing will be required to understand the subclassification of ACAOS.

Substrate for Arrhythmia

Up to 66% of diagnosed ACAOS patients do not report any symptoms (5) and the initial presentation may be sudden cardiac death (71). Thus, diagnostic evaluation should not only obtain evidence for ischemia (which can in turn induce arrhythmia), but also assess possible underlying arrhythmogenic myocardial fibrosis and scar. The latter is suspected to occur in ACAOS as an expression of recurrent minor myocardial ischemia that may serve as the substrate for ventricular tachyarrhythmias (8, 67, 69, 72). Autopsy series demonstrated myocardial fibrosis in a significant number of patients with ACAOS (8). However, the amount of fibrosis that should be considered critical is unknown, as well as the best technique to image such lesions. The management of these patients remains difficult, as it is doubtful whether those with ACAOS and myocardial fibrosis are safe to return to competitive sports after revascularization of the anomaly.

DIAGNOSTIC MODALITIES

Considering the complex pathomechanisms of myocardial ischemia in patients with ACAOS, the optimal diagnostic modality is not only expected to detect the presence of ACAOS with high accuracy but also to collect additional information on anatomical high-risk features, ischemia, evidence for possible myocardial fibrosis/scar as substrate for ventricular tachyarrhythmias (8) and concomitant CAD (34). Thus, multimodality imaging is necessary to cover this broad range of diagnostic entitlements (5, 22). **Table 2** provides an overview of the common methods.

Electrocardiogram

The standard 12-lead electrocardiogram (ECG) is a valuable diagnostic modality and important part in daily clinical workup. However, it does not play a role suspect or recognize ACAOS (73). As shown in several reports, resting ECG, even in symptomatic patients, does not show any typical alternations (8, 74–76). Similarly, stress ECG, which has already a limited diagnostic accuracy for the diagnosis of CAD [sensitivity 68%, specificity 77% (77)], is not reliable for the detection of ACAOS-dependent myocardial ischemia (8, 71, 75, 78, 79). If stress ECG may play a role by reproducing symptoms or arrhythmia is unclear (80).

Echocardiography

Using transthoracic echocardiography (TTE), the origin and the proximal course of the coronary arteries can be assessed non-invasively without radiation exposure (81, 82). Usually, diagnosis by TTE is made from a short-axis view in the plane of the aortic root including focused color Doppler interrogation of the aortic wall to identify an intramural course (52, 83). Furthermore, TTE allows the assessment of ventricular and valvular function as well as evaluation of concomitant congenital heart defects. Taking into account the general good acoustic window in children, TTE is an optimal diagnostic modality for an initial evaluation in a pediatric population, in whom radiation exposure is an issue (14, 61, 76, 84, 85). However, important limitations of TTE are the decreased diagnostic value in adults or patients with limited acoustic window (86) as well as the required experience, resulting in a substantial interobserver variability. This variability was demonstrated in a multicenter study where agreement between the echocardiographic core laboratory and the participating sites was poor (87). For the identification of anatomic high-risk features, higher resolution transesophageal echocardiography (TEE) is needed (81). Functional relevance of ACAOS can be assessed by TTE using either a physical or a pharmacological (usually dobutamine) stress looking at qualitative wall motion changes as an indirect marker for myocardial ischemia in the ACAOS subtended territories (71). However, the distal segments of the coronary arteries are not visible and therefore coronary dominance of the non-anomalous vs. anomalous vessel is not possible.

Coronary Computed Tomography Angiography

With the substantial technical advances in the last decades, coronary computed tomography angiography (CCTA) has become the preferred imaging modality for anatomic definition of ACAOS in adults (5, 22). CCTA provides the best non-invasive spatial resolution and advanced post-processing methods as 3D virtual angiographic view enable the detailed evaluation of the anatomic high-risk features (28, 36, 45, 47, 74, 88–94). In addition and especially relevant in adult patients (34), CCTA allows the

TABLE 2 | Overview of the diagnostic modalities for the assessment of ACAOS.

	Echocardiography	CCTA	CMR	ICA with IVUS/FFR	SPECT	PET
Physical characteristics						
Spatial resolution	++	+++	++	++++	+	+
Temporal resolution	++/+++*	++	++	+++	+	+
Anatomy of coronary arteries						
Proximal	+++	++++	++++	+++	-	-
Distal	++	++++	++	+++	-	-
Assessment of vascular territories	-	+++	++	+	-	-
Anatomic high-risk features in ACAOS						
Interarterial course	++	++++	++++	++	-	-
Fixed components						
Slit-like ostium	+	++++	++	+++	-	-
Proximal narrowing	++	+++	++	++++	-	-
Dynamic components						
Take-off angle	++	++++	++++	+	-	-
Elliptic shape	++	+++	++	++++	-	-
Intramural course	++	++++	+++	++++	-	-
Physiologic high-risk consequences in ACAOS						
Ischemia	++°	+**	++++	+++++	+++°	++++°
Scar	+	++	++++	-	+++	+++
Features in patients <30 years						
Feasibility in children	++++	++	+++	+	++	++
Other concomitant congenital malformations	+++	-	++++	-	-	-
Features in patients >30 years						
Evaluation of CAD	-	+++	-	++++	-	-
Cardiac function	+++	(+)	++++	++	+	++
Procedural circumstances						
Ionizing radiation exposure	-	+	-	++	+++	+++
Required expertise	++++	++	+++	+++++	+++	+++
Duration	++	+	+++	++++	++	++

**with transesophageal echocardiography; **with CT FFR or possibly CT stress perfusion; °physical exercise possible.*

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; IVUS, intravascular ultrasound; FFR, fractional flow reserve; SPECT, single-photon emission computed tomography; PET, positron emission tomography.

Please note, highest level of evidence for the guideline recommendation is "I B" for all diagnostic modalities (14, 16–18).

Adapted from Gräni C. et al. (22).

evaluation of the full course of the coronary arteries including detection of concomitant atherosclerotic CAD. In recent years, radiation exposure during CCTA has been dramatically reduced to an average of around 0.5–3 mSv in daily clinical practice (95). So far, CCTA was limited to the anatomical assessment of ACAOS. However, a novel technique may overcome this shortcoming by using computed fluid dynamic analysis, i.e., the implementation of CT fractional flow reserve (CT_{FFR}) (96, 97) in patients with ACAOS (98). While first results are promising (98–101), CT_{FFR} has been primarily used in the evaluation of CAD and its diagnostic value in other setting remains unclear. To which degree CT perfusion (using dobutamine) may play a role in assessing ACAOS needs to be determined (102).

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) imaging offers tomographic 3D imaging at high spatial resolution [slightly lower than CCTA (22, 54, 88)] without radiation at the expense of prolonged scan times and higher costs (5). It allows the visualization and assessment of the origin and the course of the ACAOS in relation to the great vessels in detail and without the use of contrast agents, rendering this modality especially attractive in the pediatric population (74, 103–105). CMR is able to capture additional relevant information related to cardiac structures and function (22), including myocardial necrosis as substrate for ventricular tachyarrhythmias (8). However, CMR is limited by its difficulty to assess the distal segments of the coronary arteries, as well as concomitant CAD. Concerning functional ischemia testing, CMR allows to investigate the hemodynamic relevance by pharmacologic inotropic stress (i.e., dobutamine) (106, 107) with a higher accuracy than stress echocardiography (108).

Nuclear Cardiac Imaging

Nuclear cardiac imaging modalities [i.e., single-photon emission computed tomography (SPECT) and positron emission tomography (PET)] are established techniques for risk

stratification and assessment of myocardial perfusion in the setting of CAD. Multiple studies used these modalities for the assessment of hemodynamic relevance of ACAOS (34, 75, 88, 109–111) and demonstrated favorable diagnostic performance. Furthermore, combination with CT allows the allocation to the corresponding vessel territory, a situation often altered in ACAOS (34, 109). However, as shown by a recent case report from our group (30), the limited spatial resolution may lead to undetected ischemia, in particular in cases with primary subendocardial ischemia.

Invasive Coronary Angiography

Invasive coronary angiography (ICA) has been the gold standard for the diagnostic of CAAs for several decades. However, it is less suited to visualize anatomic high-risk features and to determine the ACAOS course in relation to the great vessels. Owing to the advent of non-invasive imaging modalities as CCTA and CMR, ICA is no longer a first-line modality to define the anatomy of ACAOS (75, 112). Nevertheless, in combination with intravascular diagnostic procedures such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), ICA continues to have clinical significance. According to Angelini et al., IVUS is the gold standard for the assessment of the intramural segment since it allows the best spatial assessment as well as the demonstration of dynamic lateral compression during simulated exercise (46, 54). Both, determination of the pressure gradient (i.e., FFR) across the anomalous segment as well as IVUS, are possible under simulation of physical exercise, allowing the most comprehensive evaluation of the hemodynamic relevance to date (27, 56–59, 66, 113, 114). Moreover, non-invasive functional testing does not allow to uncover possible isolated right ventricular ischemia (e.g., in R- ACAOS with a small RCA and left coronary dominance), as only the left myocardium can be assessed. Although, the myocardium at risk might be rather small in these situations, one could argue that arrhythmias still can be induced from the right ventricle and should be assessed using invasive FFR.

Stress Testing

The ideal stress test for ACAOS should be able to assess both dynamic and fixed components, and has to be strenuous enough to provoke lateral compression. This requirement was illustratively demonstrated in a case report by Lim et al. (67), describing a 14-years old female patient with L-ACAOS that showed similar $FFR_{Adenosine}$ and $FFR_{Dobutamine}$ (0.87 vs. 0.86) values at a heart rate of 153 bpm (74% of the maximal heart rate) and thus, only evaluation of the fixed component. Hence, maximal exercise load is crucial and the examiners should aim for maximal or supramaximal stress (100% of predicted maximal heart rate or above, estimated with the formula of 220–age). Unfortunately, most performed stress tests were satisfied with 85% of the maximal heart rate (34, 56, 75, 111, 115), providing a possible explanation for the low reliability and the missing correlation with clinical symptoms and prognosis (46). **Table 3** provides an overview of commonly used stress protocols and their application in non-invasive and invasive diagnostic modalities. In general, maximal physical exercise should be preferred. However, this is often not feasible, especially in the invasive setting. Further, pure vasodilators (i.e., adenosine or regadenosone) are not able to provoke the dynamic components (i.e., dynamic lateral compression of the intramural course) and thus, are prone to provide false negative results. In a small case series, the lateral compression illustrated by IVUS during ICA was provoked with norepinephrine (59). However, this method does not simulate vigorous physical exercise adequately because of only slightly increased heart rate and inadequate adaption of coronary vascular resistance (116).

For invasive stress testing, Angelini et al. introduced a "SAD"-test, that entails a pharmacologic stress test with rapid infusion of 500 ml saline, dobutamine stepwise infusion up to 40 μg/kg/min and in addition 0.5 mg atropine if the heart rate is below 140 bpm at the end of the dobutamine infusion (46, 54). While this stress protocol is the closest equivalent to vigorous exercise, it has two major limitations. First, a fixed target heart rate of 140 bpm lacks age-related adaption and thus, leads to insufficient exercise load among younger patients. Second, infusion of saline is necessary, since dobutamine decreases the preload and hence, systolic arterial blood pressure, aortic wall stress and myocardial oxygen consumption. However, as with the fixed heart rate, infusion of saline should have the extent to prevent blood pressure decrease during infusion of the dobutamine and maintaining an adequate preload rather than a fixed value.

Thus, our specialized clinic for ACAOS applies a more aggressive approach with steady infusion of saline during the whole invasive procedure (usually more than 1'500 ml of saline to prevent a preload decrease) and attempts to reach 100% of the maximal heart rate, i.e., using atropine in addition to the ongoing dobutamine infusion to simulate vigorous physical exercise at the upper limit. The dobutamine and volume challenge is, of course, not practicable for every patient but should be aimed for in order to simulate maximal physical exercise and obtain conclusive results even in absence of ischemia (i.e., true-negative results).

Regarding the invasive diagnostic procedure, radial access represents the preferred access site. The intubation of the anomalous ostium in combination with advanced diagnostic including FFR and intravascular imaging under rest and stress condition requires a high level of experience and should be reserved for experienced interventional cardiologists. Potential but rare risks include aortic or coronary dissections and stroke.

Diagnostic Management of Patients With ACAOS

After detailed recording of the medical history including symptoms, physical activities and strenuous exercise related symptoms, we propose the following downstream testing algorithm (i.e., summarized in a flow chart in **Figure 3**) in individuals with suspected or confirmed ACAOS. We divided the population into those below and above 30 years according to the studies by Taylor et al. (24, 38). We are fully aware that this

TABLE 3 | Overview of possible stress protocols in assessing patients with ACAOS.

	Physical exercise		Adenosine	Regadenoson	Norepinephrine	Dobutamine	Dobutamine + volume challenge
Protocol/dose	85% of max. HR	100% of max. HR	140 μg/kg/min	Bolus: 400 μg	0.01 μg/kg/min	40 μg/kg/min	40 μg/kg/min + saline: 1.5–3 l+ atropine: 1 mg
Applied in	Non-invasive testing	Non-invasive testing	Non-invasive / invasive testing	Non-invasive testing	Invasive testing	Non-invasive / invasive testing	Invasive testing
Increase in coronary blood flow to detect relevant fixed stenosis	+ + +	+ + + + +	+ + +	+ + +	+ +	+ + ++	+ + ++
Increased heart minute volume to provoke dynamic lateral compression	+ +	+ + + + +	-	-	+ + +	+ +	+ + ++
Reproducibility of symptoms	+ + +	+ + + + +	-	-	+ +	+ +	+ + +
Tolerability	+ + ++	+ + ++	+ +	+ + +	+ +	+ +	+ +

HR, heart rate.

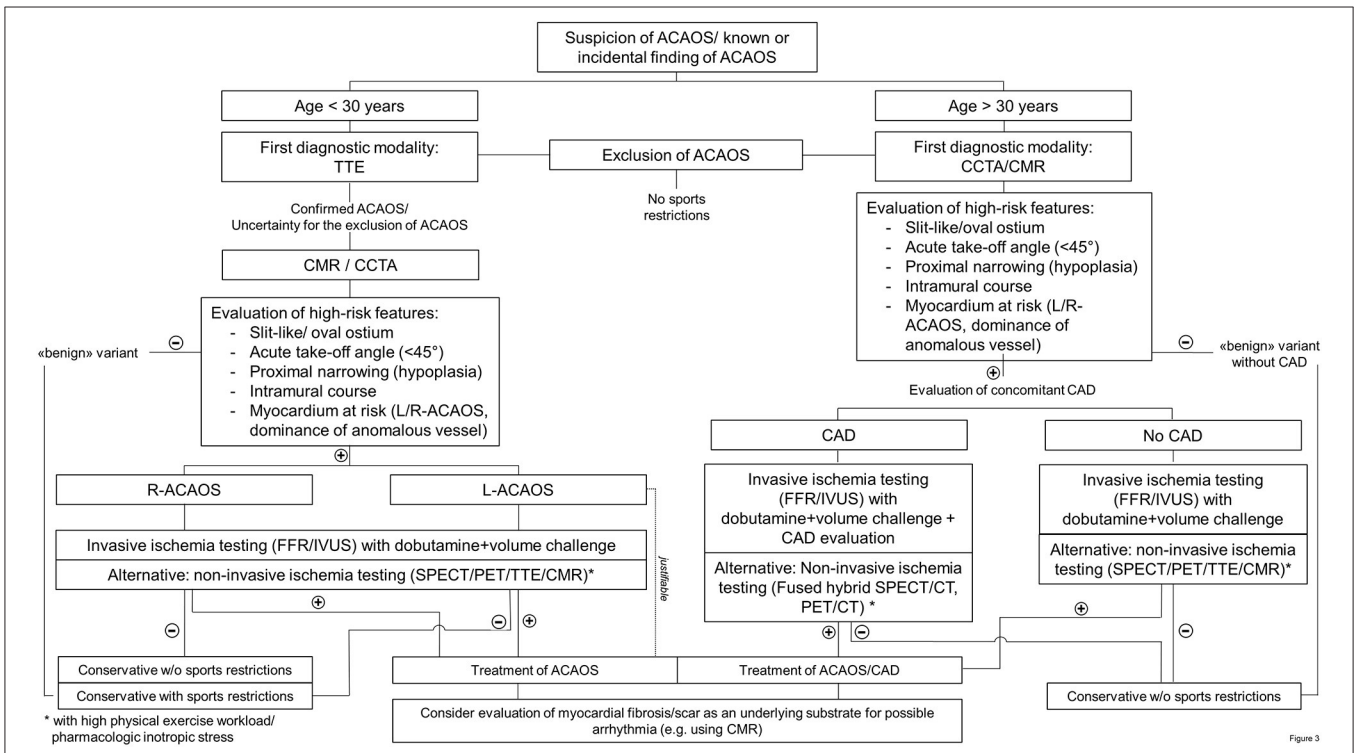

FIGURE 3 | Flow chart of diagnostic management in patients with an anomalous coronary artery. (R-/L)-ACAOS, (right/left) anomalous coronary arteries with the origin of the anomalous vessel from the opposite sinus of Valsalva; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance imaging; FFR, fractional flow reserve; IVUS, intravascular ultrasound; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography.

dichotomization is arbitrary and should not be seen as a stringent recommendation but is rather meant for guidance.

Patients Under 30 Years of Age

In patients under 30 years of age (and especially in the pediatric population), the initial diagnostic modality should be TTE by an experienced sonographer. If ACAOS cannot be ruled out with certainty (because of inexperience, low acoustic window quality and/or others) or in cases where ACAOS is confirmed, additional imaging is required. For the subsequent diagnostic step, CCTA or CMR are the recommended diagnostic modalities, based on the local expertise

and availability. Using these imaging methods, evaluation of anatomic high-risk features is crucial to directly rule out "benign" variants of CAA. Thus, ACAOS without any anatomic high-risk features can be safely deferred (5, 22), respectively referred to for further evaluations of the underlying causes in symptomatic patients.

Non-invasive functional testing is recommend when considering the association of cardiovascular events in ACAOS with strenuous exercise. This is, however, only useful when turning out positive or as reference value for subsequent evaluations. As stated by Cheezum et al., "the absence of ischemia during stress testing cannot be viewed as reassuring currently, particularly when potentially high-risk anatomic features are present" (5). In addition, we propose that every ACAOS with anatomic high-risk features should undergo an invasive evaluation of the hemodynamic relevance including assessment of IVUS and FFR under a dobutamine and volume challenge and non-invasive imaging should rather be seen as an alternative. If there is no evidence for ischemia and the patient remained asymptomatic, a conservative approach should be justifiable. In the other situations, revascularization should be recommend (14, 16) as well as a CMR (if not already done) for the evaluation of patchy myocardial necrosis.

Patients Over 30 Years of Age

In patients over 30 years of age, the diagnostic scheme is similar. However, in this setting, concomitant CAD must be ruled out. Accordingly, first-line modality is CCTA, followed by the same diagnostic procedures as outline above. Please note, even if TTE is not recommended as first-line modality in this population, we believe that it is an integral part of a cardiac diagnostic workup in adult people (similar to the ECG).

GAPS OF KNOWLEDGE

Multiple gaps of knowledge exists in ACAOS regarding the optimal diagnostic evaluation, risk stratification and management. As outlined by Brothers et al., we are not yet able to distinguish which individuals and which variants of ACAOS are at high risk for ischemia and who should we refer for revascularization (14).

The main questions are:

1. What is the prognosis of patients with only few/milder versions of anatomical high-risk features (e.g., short intramural course)? What are cut-off values for acute take-off angle, intramural length, height-width ratio of the slit like ostium that associated with an increased risk for adverse cardiac outcomes?
2. Does the decreased risk for SCD in newly detected ACAOS in older people represents a selection-bias toward a low-risk population (higher-risk individuals died at a younger age) or does the normal development in this patient cohorts based on pathophysiologic alternation (e.g., increased stiffness of the aortic wall) lead to a decreased lateral dynamic compression of the anomalous segment?
3. Does discrepancy between different invasive hemodynamic parameters [systolic/diastolic, resting and stress parameters (117)] represent valuable information on the aortic wall distensibility and the hemodynamic relevance?
4. Are sports restriction recommendations (dynamic vs. static sports, recreation vs. competitive sports) and revascularization necessary for all patients with high-risk features? What is the relevance of the age and the symptomatic burden on sports counseling?
5. Is it possible to predict the hemodynamic relevance of ACAOS purely based on non-invasive anatomical description of the high-risk features?

Ongoing studies:

Currently, several single site and multinational registries (118, 119) are recruiting patients to address the remaining gaps. Our site currently recruits patients for the systematic evaluation of ACAOS (NCT04475289) including non-invasive imaging (CCTA, stress-testing) as well as comprehensive invasive functional assessment. Our hypothesis is that the exact description of the anatomical features in the CCTA can determine the hemodynamic relevance of ACAOS using the invasively measured $FFR_{Dobutamine}$ as reference.

CONCLUSION

Despite numerous efforts to uncover the enigma of the hemodynamic relevance in patients with ACAOS, our understanding of the complex interactions leading to myocardial ischemia, remains unsatisfactory. Due to the low prevalence in the general population, major efforts have to be made to collect data from multinational ACAOS registries to better understand the pathophysiology of this entity. We advocate a two-tier concept, where the hemodynamic relevance of ACAOS is represented by a fixed component (e.g., proximal narrowing; similar to CAD) and a dynamic component (e.g., lateral compression), accentuated during exercise, providing explanations for the various clinical presentations. Hence, comprehensively assessment of the hemodynamic relevance of ACAOS should contain multimodality non-invasive and invasive imaging with adequate stress testing.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Sudden Death and Coronary Artery Anomalies

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Congenital coronary artery anomalies (CAA) include a wide spectrum of malformations present at birth with various clinical manifestations and degrees of severity. Patients may be asymptomatic, and CAA may be an incidental finding during cardiac imaging or at autopsy. However, in other cases, ischemia-related signs and symptoms, leading to an increased risk of sudden cardiac death (SCD), often as first presentation may occur. In this chapter, we discuss the normal anatomy of the coronary arteries (CA) and the pathology of CAA at risk of SCD, including our experience with victims of SCD among the young population (age <40 years) and among athletes.

Keywords: coronary anomalies, pathology, sudden death, diagnosis, surgical procedures

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NORMAL ANATOMY OF THE CORONARY ARTERIES (CA)

Normally, two main CA, the right (RCA) and the left main (LCA), the latter branching into the left circumflex artery (LCX) and the left anterior descending artery (LAD), arise from the aortic right anterior and left anterior sinuses of Valsalva, respectively, close to the sino-tubular junction, without any relation to the pulmonary trunk. Variations on normal anatomy are the separate origin of the conal artery and RCA from the right coronary sinus as well as that of the LCX and the LAD from the left coronary sinus. A coronary ostium may originate from a higher position, up to 2.5 mm at maximum, compared to the normal site at the sino-tubular junction (1). Coronary dominance (right, left, co-dominant circulation) is also considered a variation of the normal. The main CA normally run in the subepicardium of the atrioventricular and interventricular grooves, dividing into branches which supply the atria and the ventricles.

CORONARY ARTERY ANOMALY (CAA)

CAA is a rare disorder, reported in <1% of the general population on the basis of coronary imaging techniques and autopsy (2, 3). Although rare, CAA might precipitate myocardial ischemia at risk of sudden cardiac death (SCD), even in the young and in athletes.

Several classifications have been proposed for CAA (3, 4). The classification by Angelini (4) is based on anatomical features, and three categories are recognized: anomalies of origin and course; anomalies of intrinsic CA anatomy; and anomalies of coronary termination.

While anomalies of origin and course will be discussed in depth because of their potential link to SCD, anomalies of intrinsic CA anatomy and termination will be briefly commented on. The latter includes ostial stenosis/atresia and hypoplasia. CA ostial stenosis/atresia is an extremely rare anomaly leading to collateral vessels formation from the normal CA, usually inadequate for

satisfying myocardial oxygen demand. The clinical presentation is usually in the first year of life. Hypoplastic CA refers to a narrowed lumen (<1.5 mm) of one or two of the three main epicardial CA (5). However, caution should be used not to confound extreme right or left dominant patterns with CA hypoplasia.

Anomalies of coronary termination correspond to coronary fistulae, characterized by a connection between the CA and a cardiac chamber or intrathoracic great vessel, leading to left-to-right shunts and myocardial ischemia. Moreover, termination in a low-pressure space causes enlargement and tortuosity of the fistulous CA at risk of aneurysmatic dilatation and rupture (6).

While in the past these CAA could only be described at autopsy, currently they can be effectively detected with non-invasive diagnostic imaging, thanks to enormous technological advancements.

The most practical non-invasive diagnostic tool is transthoracic two-dimensional echocardiography, which in experienced hands can identify these anomalous origins *in vivo* with a good sensivity, although it remains more effective and easier in the pediatric population. Transesophageal echocardiography is much more sensitive but is a semi-invasive tool. However, nowadays, axial computed tomography (CT) and/or magnetic resonance (MR) imaging are reliable non-invasive tools for diagnosing CAA and are proposed and accepted worldwide as the gold standard for the identification of an anomalous origin and course. Last, but not least, cardiac stress test and myocardial scintigraphy are complementary investigations that may help in assessing the functional status, and guide surgical indication.

CAA AND SCD: RISK IS NOT THE SAME FOR ALL

According to the autopsy guidelines for the study of SCD of the Association for European Cardiovascular Pathology (7), the degrees of certainty (i.e., certain, highly probable, or uncertain) in defining the causative role of various CAA in SCD are different, along with the recommendations for management and sport eligibility. Only the origin from the pulmonary trunk is considered as a certain cause, with the origin of LCA from the opposite right sinus of Valsalva considered as a highly probable cause and the remaining (RCA from left, LCX from right and retroaortic course, high take off and myocardial bridge) considered as uncertain causes of SCD.

Anomalous Origin of CA From the Opposite Aortic Sinus

The anomalous origin of a CA from the contralateral sinus of Valsalva (also known as anomalous aortic origin of CA) is the most common life-threatening anomaly associated with an increased risk of SCD, especially when the CAA has a proximal intramural and interarterial course between the aorta and the pulmonary artery (8–11). According to the proximal course of the anomalous CA, there are four subtypes: anterior to the pulmonary trunk (pre-pulmonic), posterior to the aorta (retroaortic), septal (sub-pulmonic), or between the pulmonary artery and the aorta (interarterial). The latter has been associated with an increased risk of SCD, especially in young athletes. Several explanations have been proposed: a slit-like lumen of the anomalous CA (11), an associated intramural course of the anomalous CA within the aortic wall, and a compression between the aortic root and the pulmonary trunk under effort, resulting in ischemia (11, 12). Barth and Roberts reported that in 38 autopsy patients with an LCA arising from the right aortic sinus with an interarterial course, 29 died suddenly in the first two decades of life and 28 during exercise (13). The origin of the LCA from the right sinus is considered more malignant, probably because of the wider myocardial territory at risk of ischemia. However, both RCA and LCA origins from the contralateral sinus increase the risk of SCD (**Figure 1**) (14). SCD may be the first manifestation of the disease, although patients may present with symptoms like syncope or chest pain (15–17). Moreover, myocardial necrosis and replacement-type fibrosis can trigger life-threatening ventricular arrhythmias. The anomalous origin of the LCA from the posterior aortic sinus is quite rare but may be associated with SCD as well.

The anomalous origin of the LCX from the right sinus of Valsalva or from the RCA is the second most common CAA (15), usually considered a benign condition since the course of the ectopic LCX is retroaortic. However, under effort, lumen stenosis due to compression by the dilated aortic root may occur. Cases of ischemia-related cardiovascular events, and less commonly unexpected arrhythmic SCD, have been described (7, 11).

Anomalous Origin of CA From the Pulmonary Artery

An anomalous origin of the LCA from the pulmonary artery (ALCAPA), also called Bland-White-Garland syndrome (18), is a rare but potentially life-threatening CAA, characterized by a reverse flow into the pulmonary artery. An anomalous origin of the RCA from the pulmonary artery, or ARCAPA, is less frequent (19, 20). Most patients, if untreated and undiagnosed, develop myocardial ischemia and heart failure in infancy, and usually die within the first year of life. In fact, as pulmonary vascular resistances decrease physiologically, there is a reduction of the flow in the LCA. However, occasionally some patients may remain asymptomatic and survive into adulthood (21, 22). Depending on collateral vessels growth, we recognize two types of ALCAPA: the "adult type" with well-developed collaterals (23) and the "infant type" with poor collaterals and early onset of symptoms when pulmonary arterial pressure decreases. Although SCD may occur (24), the usual and most common clinical manifestation of ALCAPA is congestive heart failure.

Single CA

This is a very rare condition in which only one CA arises from the aorta. A single CA may originate either from the left or the right Valsalva sinus and may coexist with other congenital anomalies. The single CA may take the course of either an RCA or an LCA and divide shortly from its origin into two or three of the main coronary branches. Lipton et al. (25) proposed an anatomical classification of single CA based on the location

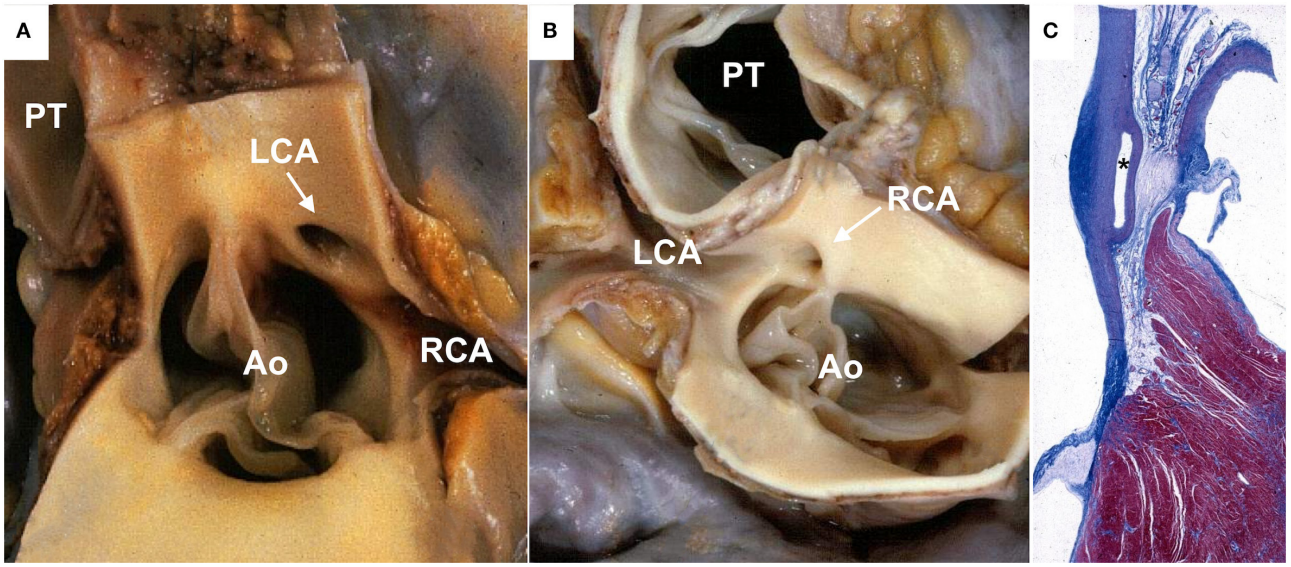

FIGURE 1 | Anomalous origin of a coronary artery from the contralateral aortic sinus in sudden cardiac death cases. **(A)** Gross view of heart specimen showing the left coronary artery arising from the right aortic sinus close to the right coronary ostium (arrows) with a slit-like lumen. **(B)** Gross view of heart specimen showing the right coronary artery arising from the left aortic sinus, close to the left coronary ostium (arrow). **(C)** Histologic section showing the interarterial course of the left coronary artery between the aorta and the pulmonary trunk (asterisk). Ao, aorta; LCA, left coronary artery; PT, pulmonary trunk; RCA, right coronary artery.

of the ostium, anatomical distribution, and course. Although single CA may be compatible with a normal life expectancy, thanks to the development of collateral branches, patients are at increased risk of myocardial ischemia and SCD when a major CA branch courses between the pulmonary artery and the aorta (26), especially when the single CA originates from the right sinus.

A STILL CONTROVERSIAL RISK FOR SCD: HIGH TAKE-OFF CA AND MYOCARDIAL BRIDGE

High Take-Off of a CA

The location of a CA ostium above the limit of 2.5 mm (1) has been observed in unexplained SCD, especially when the ostium is funnel-like with a narrowed lumen, and the course is intra-aortic before reaching the aortic root and then the atrioventricular (AV) sulcus (27–29). Intramural aortic course and compression during aortic dilatation under effort may account for lumen stenosis and inadequate myocardial supply. However, the clinical significance of this anomaly remains controversial (7).

Myocardial Bridge

This condition is a pure anomaly of the coronary course, while the origin and ostial features are usually perfectly normal. There are some doubts whether myocardial bridge constitute an anomaly or a normal variant, according to its frequency in the general population in imaging or autopsy studies (30). A myocardial bridge is defined as an atypical course of a CA intramyocardially, usually the proximal and mid-segment of the LAD, which may result in compression of the vessel during systole (milking effect) (**Figure 2**). Myocardial bridge may lead to ischemia, when characterized by a deeper (5 mm) and longer (2–3 cm) intramyocardial course, with the myocardium encircling the intramural segment acting like a sphincter (31, 32).

Myocardial bridge is found frequently in patients with hypertrophic cardiomyopathy (HCM), with a prevalence of up to 30% (33), representing a possible cause of ischemia and SCD (34) due to systolic lumen obliteration, but also persistent occlusion during diastole, as a result of impaired relaxation of the myocardium surrounding the anomalous segment. Although SCD has been ascribed to myocardial bridge in young people and in athletes, this feature is nowadays classified among the uncertain causes of SCD (7).

MANAGEMENT OF ASYMPTOMATIC PATIENTS AND INDICATION FOR SURGERY

Wrong Sinus Origin CAA

The incidental finding of a wrong sinus origin CAA *in vivo* is increasing due to the large use of non-invasive coronary artery imaging techniques or during angiography performed to detect atherosclerotic CA disease. This incidental diagnosis has a great impact on the management (medical treatment, interventional, or surgical repair) and the risk stratification of these patients. Most variants are benign. The best treatment for CAA is still debated, and a multidisciplinary approach is mandatory.

Moreover, after a CAA of wrong sinus origin is identified, clinical management should be based on nuclear stress coronary angiography to evaluate for the presence of atherosclerotic disease, and an intravascular ultrasound (IVUS) of the

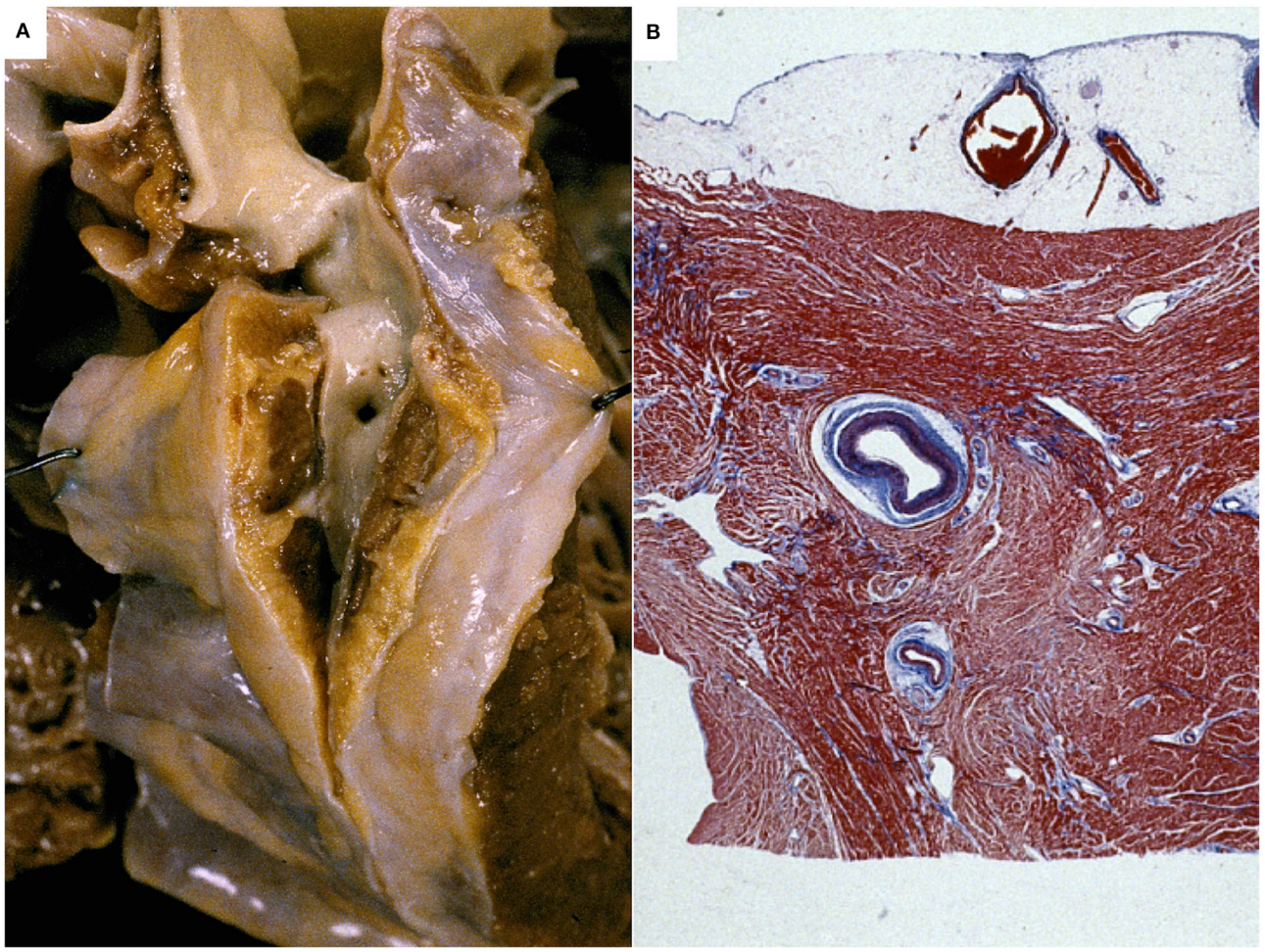

FIGURE 2 | Myocardial bridge of the left coronary artery in an sudden cardiac death case. A segment of the left coronary artery runs deep in the myocardium. Gross view of the heart **(A)** and histology (Heidenhain stain) **(B)**.

anomalous vessel. A grading of the CAA according to IVUS criteria has been proposed, by considering the amount of hypoplasia and the degree of lateral compression of the proximal vessel. Assessment of the fractional flow reserve (FFR) is also recommended together with IVUS, both at baseline and with dobutamine pharmacological stress. Cheezum et al. (35) published a useful comparison of all available anatomic tests used to characterize CAA. Moreover, while recognizing the potential values of ischemia provocative tests to assess the functional significance of CAA, a review of published data demonstrates that both exercise treadmill testing and stress myocardial perfusion imaging may yield false-positive and false-negative results. It is worthy to note that among the 27 young athletes who died suddenly with interarterial wrong sinus CAA reported by our group (11), six patients had a normal exercise treadmill test.

Guidelines (36, 37) recommend surgery (class I) in cases of CAA from the left or right sinus when it is associated with cardiac symptoms, or diagnostic evidence of stress-induced ischemia in the matching territory, or with high-risk coronary anatomy. Revascularization is also recommended for interarterial anomalous origin of the LCA, regardless of ischemia or symptoms. Despite these recommendations, the optimal management of patients with interarterial CAA is still debated. In a recent series of 66 middle-aged individuals with newly diagnosed CAA, mid-term outcome was not statistically different to a matched control cohort without CAA, regardless of whether CAA with or without interarterial course were present (38).

According to Cheezum et al. (35), in all cases of clinically suspected interarterial wrong sinus CAA, imaging with CT or MR is recommended to visualize anatomic features such as the proximal vessel obstruction that may guide surgical decision making. While in anomalous LCA with interarterial course surgical treatment should be always discussed, a conservative approach is reasonable in asymptomatic individuals with anomalous RCA with interarterial course, no proximal vessel narrowing, and no evidence of ischemia. The optimal

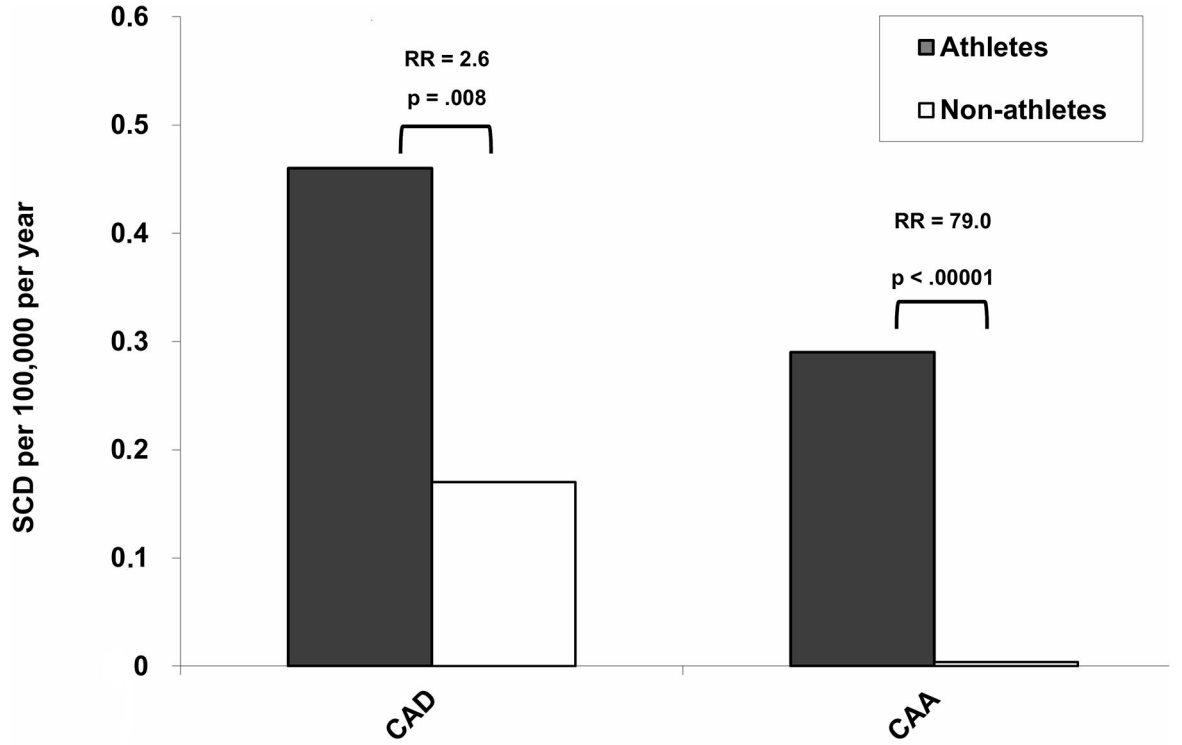

FIGURE 3 | Incidence and relative risk (RR) for sudden cardiac death (SCD) for atherosclerotic coronary artery disease (CAD) and coronary artery anomalies (CAA) among athletes and non-athletes [modified from Corrado et al. (52)].

management strategy likely varies as a function of individual age, presentation, anatomy, and physiology.

Anomalous Origin of CA From the Pulmonary Artery

In this setting, surgical repair (mostly by reimplantation of the anomalous CA on the aortic root) is considered mandatory as soon as instrumental diagnosis is finalized (39). Concomitant repair of ischemic mitral regurgitation is usually not indicated unless anatomical abnormalities are associated. Even though left ventricular wall motion abnormalities, perfusion deficits, and myocardial scarring may remain in many patients, myocardial function improvement is expected in most cases within a few years after repair, if this was performed early in infancy (40).

Myocardial Bridge

The major challenge is again the functional assessment for decision making when dealing with the incidental finding of myocardial bridge by angiography ("milking effect") and/or CT (41).

Stress single-photon emission CT can detect reversible myocardial perfusion defects in those patients, with a correlation between the amount of ischemia and the degree of systolic luminal narrowing.

Coronary physiological measurements during pharmacological infusion are also helpful.

Imaging by IVUS can reveal the characteristic "half-moon" sign, an echolucent area between the bridged coronary segment and epicardial tissue that persists throughout the cardiac cycle. However, both in symptomatic patients and in those with an "incidental" finding by angiography or CT, there is no consensus whether further diagnostic studies of myocardial bridge are needed before therapy.

RECOMMENDATIONS FOR SPORT ACTIVITY IN ATHLETES WITH CAA

Official consensus guidelines for eligibility/disqualification decisions in competitive athletes with CAA are available at international and at national levels (42, 43).

In the recent European Society of Cardiology (ESC) 2020 Guidelines on sports cardiology and exercise in patients with cardiovascular disease, evaluation with imaging tests to identify high-risk patterns and an exercise stress test to check for ischemia is recommended in individuals with either left or right wrong sinus CAA (class IIa, level C).

In asymptomatic individuals with wrong sinus CAA without interarterial course or a slit-like orifice with reduced lumen and/or intramural course, competition may be considered, after adequate counseling on the risks, provided there is absence of inducible ischemia (class IIb, level C). After surgical repair, sport participation may be considered 3 months after surgery,

TABLE 1 | Prevalence of CAA in major (≥100 cases) autopsy series of sudden cardiac death in the young.

Authors (Reference)	Year	Time	Location	Population	Age	N. SCD	Sex, *M* (%)	CAA, *N* (%)
Burke et al. (9)	1991	1981–1988	Maryland, United States	Athletes Non athletes	14–40	34 656	31 (91) 501 (76)	4 (12) 8 (1.2))
Drory et al. (53)	1991	1976–1985	Israel	General	9–39	162	134 (82.7)	1 (0.6)
Corrado et al. (52)	2003	1979–1999	Veneto region, Italy	Athletes Non athletes	1–35	55 245	50 (90.9) 170 (69.3)	9 (16.3) 5 (2)
Van Camp et al. (54)	1995	1983–1993	US high schools and colleges	Athletes	13–22	100	92 (92)	16 (16)
Maron et al. (46)	1996	1985–1995	United States	Athletes	<35	134	120 (89.5)	31 (23.1)
Wisten et al. (55)	2002	1992–1999	Swedish	General	15–35	181	132 (72.9)	7 (3.9)
Morentin et al. (56)	2003	1991–1998	Bizkaia county, Spain	General	1–35	107	ND	ND
Doolan et al. (57)	2004	1994–2002	New South Wales, Sydney, Australia	General	< 35	193	125 (64.7)	ND
Eckart et al. (58)	2004	1977–2001	Brooke Army Medical Center, San Antonio, Texas, United States	General	18–35	126	111 (88.1)	21 (16.7)
Puranik et al. (59)	2005	1995–2004	Eastern part of Sydney, Australia	General	5–35	241	189 (78.4)	5 (2.1)
Di Gioia et al. (60)	2006	2001–2005	Lazio region, Italy	General	1–35	100	69 (69)	4 (4)
Maron et al. (49)	2009	1980–2006	United States	Athletes	13–25	1049	937 (89.3)	119 (11.3)
Eckart et al. (62)	2011	1998–2008	Personnel from the Department of Defense, United States	General	18–35	298	282 (94.6)	12 (4.0)
Margey et al. (63)	2011	2005–2007	Ireland	General	15–35	116	90 (77.5)	2 (1.7)
Winkel et al. (64)	2011	2000–2006	Denmark	General	1–35	314	210 (67)	3 (0.9)
Pilmer et al. (65)	2013	2008	Ontario, Canada	General	2–40	174	133 (76.4)	ND
de Noronha et al. (66)	2014	2007–2009	United Kingdom	General	0–35	422	ND	5 (1.2)
Risgaard et al. (67)	2014	2007 - 2009	Denmark	General	12–49	439	317 (72.2)	4 (0.9)
Bagnall et al. (68)	2016	2010–2012	Australia and New Zealand	General	1–35	490	353 (72)	ND
Maron et al. (61)	2016	1980-2011	United States	Athletes	< 35	842	747 (88.7)	158 (18.8)
Finocchiaro et al. (69)	2016	1994-2014	United Kingdom	Athletes	< 35	258	ND	13 (5.0)

SCD, sudden cardiac death; CAA, coronary artery anomaly; ND, not determinable.

at the earliest, if they are asymptomatic and there is no evidence of inducible myocardial ischemia or complex cardiac arrhythmias during maximal exercise stress tests (class IIb, level C). Participation in most competitive sports with a moderate and high cardiovascular demand among individuals with wrong sinus CAA with an acutely angled take-off or an anomalous course between the large vessels is not recommended (class III, level C) (42).

These recommendations reflect what has been written in the 2017 update of the Italian COCIS guidelines for sport activity (43). Moreover, in this document the anomalous origin of the LCX from the right is eventually mentioned separately, recognizing the benign behavior in the absence of the signs and symptoms of ischemia.

As far as myocardial bridge is concerned, the ESC guidelines say that participation in competitive and leisure-time sports should be considered in asymptomatic individuals without inducible ischemia or ventricular arrhythmia during maximal exercise testing (Class IIa, level C). Competitive sports are not recommended in individuals with myocardial bridge and persistent ischemia or complex cardiac arrhythmias during maximal exercise stress testing (class III, level C). The clinical evaluation of individuals with myocardial bridge includes the morphologic assessment of the anatomical anomaly (i.e., depth and overall length of the tunneled vessel) and the presence of inducible ischemia. A positive inotropic and positive chronotropic stress test is the best approach to demonstrate myocardial ischemia.

Such recommendations again reflect those proposed in the 2017 update of the Italian COCIS guidelines for sport activity.

Although atherosclerotic CA disease is the major determinant of acute coronary syndrome and SCD, CAA represents a significant cause of SCD in the young and in athletes, particularly in the context of exercise (9, 11, 14, 15, 44–51). In the prospective cohort study of all young people of the Veneto Region of Italy, sports activity was associated with an increased risk of SCD. In particular, sport triggered SCD in those athletes who were affected by cardiovascular conditions predisposing to ventricular arrhythmias during effort. The higher risk of SCD in athletes was strongly related to underlying cardiovascular diseases such as CAA (RR 79, CI 10 to 3,564; $p < 0.0001$) (**Figure 3**), arrhythmogenic right ventricular cardiomyopathy (RR 5.4, CI 2.5 to 11.2; $p < 0.0001$), and premature atherosclerotic CA disease (RR 2.6, CI 1.2 to 5.1; $p = 0.008$) (52) (**Figure 3**). **Table 1** lists autopsy-proven studies reporting the prevalence of CAA as the cause of SCD in the young and/or in athletes (9, 52, 55, 58, 60, 61, 63, 64, 68, 69).

Because electrocardiograms, both 12-leads basal and stress test, have a scarce sensibility, the presence of alarming signs or symptoms particularly on effort should lead to perform non-invasive and invasive imaging tools for early identification of CAA and decision about sports eligibility.

AUTHOR CONTRIBUTIONS

All authors have participated in the research and/or article preparation and approved the final article.

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REVIEW
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Surgery for Anomalous Aortic Origin of Coronary Arteries: Technical Safeguards and Pitfalls

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Anomalous aortic origin of a coronary artery (AAOCA) is reported as the second leading cause of sudden cardiac death in otherwise healthy young individuals. Several surgical studies have reported a shallow operative risk, describing repair as safe and effective with short or medium-term follow-up. However, surgical repair can also be associated with a high risk of complications. Numerous repair techniques have been described in the literature, but each technique's indications and limitations are often not well-understood or understated. Since explicit technical knowledge of the most appropriate surgical technique is highly desirable, we sought to thoroughly and clearly outline the safeguards and pitfalls of the most common surgical techniques used to repair AAOCA.

Keywords: anomalous coronary arteries, surgery, outcomes, techniques, pitfalls

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Anomalous aortic origin of a coronary artery (AAOCA) is a congenital heart defect consisting of an abnormal origin and course of a coronary artery that arises from the aorta and differs from the usual pattern (**Figure 1A**). The most common and clinically relevant anomaly is the anomalous origin from the opposite sinus of Valsalva, including the more common anomalous origin of the right coronary artery from the left aortic sinus (AAORCA, **Figure 1B**), and the more morbid anomalous origin of the left coronary artery arising from the right aortic sinus (AAOLCA, **Figure 1C**) (1).

This congenital anomaly is the second leading cause of sudden cardiac death (SCD) in otherwise healthy young adults (2–4). In the past, the diagnosis was commonly made at autopsy (5). Today, more and more children and young adults are being diagnosed incidentally based on transthoracic echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) (6). As the exact pathophysiology of AAOCA is still not well-understood, there is a lack of evidence-based guidelines addressing optimal diagnostic work-up, downstream testing, sports counseling, and therapeutic options in patients with such a congenital anomaly (7).

Single-center (8–15) and multi-center studies (16, 17) have reported shallow operative risk, describing repair as safe and effective in the short- and mid-term. Various technical procedures have been applied and reported in the literature, but the necessary minutiae of each technique are often understated, as are the postoperative complications. Emerging data (17) show that coronary-related reoperations and adverse events may occur more often than expected. Given the potentially devastating consequences of unaddressed AAOCA (i.e., SCD), counterbalanced by the

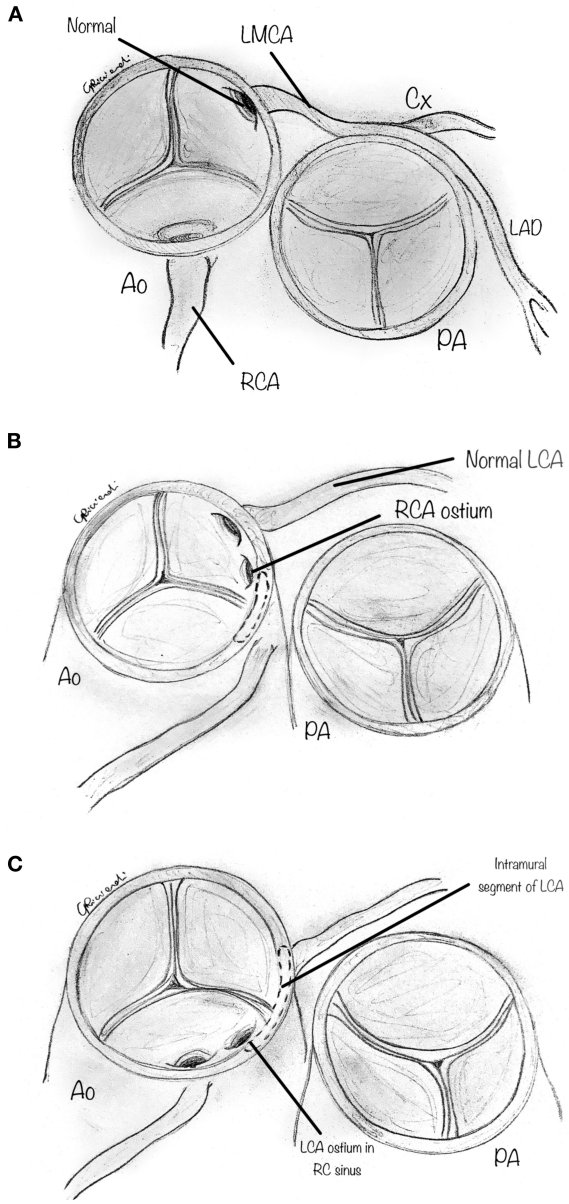

FIGURE 1 | Diagram showing cross section aortic view : **(A)** Normal coronary artery anatomy: the left main coronary artery (LMCA) gives origin to the Left anterior descending (LAD) and circumflex (CX) coronary artery, which arise from a common stem from the left aortic sinus; the right coronary artery (RCA) arises from the right aortic sinus; **(B)** the most common type, i.e., anomalous aortic origin of the RCA from the left sinus (AAORCA), with an intramural segment; **(C)** the most lethal type, i.e., anomalous aortic origin of the LCA from the left sinus (AAOLCA), with an intramural segment.

risk of iatrogenic coronary complications in the postoperative period, the optimal management strategy is still under debate (18, 19). Currently, surgery is recommended as class I, Level of evidence C, only in patients with AAOCA (either AAOLCA or AAORCA), presenting with typical angina symptoms and with evidence of stress-induced myocardial ischemia in a matching territory, or high-risk coronary anatomy (20).

However, if it is true that high-risk patients should undergo repair of the anomaly when it is discovered, absolute and precise knowledge of the most appropriate surgical technique is highly desirable. Several repair techniques have been described (8, 9, 13, 21–23), but these techniques cannot be universally applied since the optimal surgical maneuver often depends on the patient's coronary anatomy's subtle details.

We sought to describe the most common surgical procedures reported for the repair of AAOCA to outline their safeguards and pitfalls and promote such techniques' optimal utilization.

OPERATIVE TECHNIQUES

Initial Steps

The initial operative steps for all AAOCA repair techniques include standard cannulation for cardiopulmonary bypass. While minimally invasive techniques (reverse T upper mini sternotomy or posterolateral thoracotomy) are probably feasible in straight forward AAOCA, a median sternotomy is often preferred since the risk of the requirement of coronary revascularization can never be ruled out, and more convenient access to internal thoracic artery must be promptly available. After pericardiotomy, careful examination of the coronary pattern can detect all additional external features of the AAOCA. These features should be expected and confirmed in reference to the axial imaging (CT or MRI) obtained preoperatively. The surgeon should note an interarterial course, coronary take-off angle, spatial relationship to the pulmonary artery (PA), and the proximal segment's hypoplasia. A dual-stage venous cannula or bicaval venous cannulation via the superior and the inferior vena cavae can be used, if necessary, for simultaneous intracardiac operations. After aortic and venous cannulation, with full heparinization, cardiopulmonary bypass is initiated, and the cross-clamp is applied. Cold-blood anterograde del Nido Cardioplegia Solution (single shot, which protects the heart up to 180 min) is preferable since it avoids the interruption of repeated dosing during the procedure as is common with other cardioplegic solutions.

Coronary Unroofing Technique

As shown in **Table 1**, the most common surgical procedure reported in the literature for AAOCA repair is coronary unroofing (8, 9, 15, 16, 25). This is utilized when a long segment of the proximal coronary course is intramural, with a common wall between the aorta and the coronary artery. Excision of the common wall prevents coronary compression and ischemia during strenuous effort. Otherwise, when blood pressure suddenly increases as occurs with strenuous exercise, the aortic root dilates, and luminal narrowing occurs, reducing coronary perfusion (28).

After cross-clamping and infusion of the cardioplegic solution, on cardiac arrest, a transverse aortotomy is made above the commissures, about 1 cm distal to the sino-tubular junction (**Figure 2**). The aortotomy is then extended to the aortic valve's annulus, directed to the left-right intercoronary commissure. Stay sutures are placed in the distal part of the divided ascending aorta to augment the aortic root's visualization. When inspecting the aortic root, the two coronary orifices are usually visualized

TABLE 1 | Surgical series reported in literature.

Surgical series	Pts n.	Age range (years)	Technique	Early mortality (*n*, %)	Early surgical complications (*n*, %)	Follow up (years, mean/median)	Late cardiac mortality (*n*, %)	Late reinterventions (*n*, %)
Romp et al., 2003 (21)	9	7–65	Unroofing (9)	0	0	2.4	0	1 (11%) Ross operation
Gulati et al., 2007 (22)	18	0.1–16	Unroofing (11) Reimplantation (3) PA translocation (4)	0	0	2.2	0	1 (5.5%) OHT
Frommelt et al., 2011 (9)	27	4–20	Unroofing (27)	0	0	1.8	0	0
Mumtaz et al., 2011 (10)	22	5–54	Unroofing (22)	0	0	1.4	0	0
Wittlieb-Weber et al., 2014 (12)	24	5–18	Unroofing (23) Reimplantation (1)	0	0	5.25	0	0
Sharma et al., 2014 (15)	75	13–70	Unroofing (63) Unroofing + CABG (3) CABG or reimplantation (9)	0	1 (1.3%) ICD	1.56	1 (CVA)	1 (1.3%) AVR
Kooij et al., 2015 (23)	31	9–66	Unroofing (17) Unroofing + reimplantation (8) CABG (1) Ostioplasty (4) Reimplantation +IVS release (1)	0	3 (had VF postop)	6	0	0
Law et al., 2016 (24)	16	17–70	Reimplantation (16)	0	1(CABG + MVR)	5	0	1 (stent)
Mainwaring et al., 2016 (13)	115	0.1–65	Unroofing (86) Reimplantation (9) PA translocation (20)	0	0	6	0	2 (coronary)
Fabozzo et al., 2016 (14)	72	0.1–50.1	Unroofing (64) Reimplantation (8)	0	4 (6%)	1.9	0	1 (AVr)
Nees et al., 2018 (18)	60	0.3–68	Unroofing (56) Reimplantation (4)	0	0	Median 1.6	0	3 (AVR 1, Coronary in 2) ECPR for SCD
Mery et al., 2018 (8)	44	8–18	Unroofing (35) Reimplantation (7) Ostioplasty (1) Side-to-side anastomosis (1)	0	1 (2.2%) CABG	Median 2	0	1 (2.2%) repair of myocardial bridge
Sachdeva et al., 2018 (25)	63	0.5–18	Unroofing (63)	0	0	Median 3.1	1 SCD (2)	0
Ibrahhem et al., 2019 (26)	33	Mean age 34.8 + 4.6	Off Pump CABG with coronary ligation (16)	1 (3%)	0	5.25	1 (3)	1 (redo CABG on pump)
Padalino et al., 2019 (16)	156	15–53	Unroofing (88) Reimplantation (30) Ostioplasty (12) PA translocation (2) CABG (24)	2 (1.3%)	7 (4.5%)	2	3 (1.9)	3 surgical (2.3%) 6 (4.5%) interventional
Gaillard et al., 2020 (27)	61	3.7–66.1	Anatomical repair ostioplasty (37) Reimplantation (19) Intraseptal relief (5)	0	(1) ECMO and revision for thrombosis (2) Stenting	3.1	0	1 (revision for patch aneurysm)
Jegatheeswaran et al., 2020 (17)	395	9.9–15.5	Unroofing (334) Reimplantation (24) Ostioplasty (25) PA translocation (22) CABG (3) Other (14)	4/395 (1%) 3/395 (CVA)	14	2.8	0	28

ICD, implantable cardiac defibrillator; AVR, aortic valve replacement; AVr, aortic valve repair; CVA, cerebro-vascular attack; CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; ECPR, ECMO cardiopulmonary resuscitation; IVS, interventricular septum; MVR, mitral valve replacement; OHT, orthotopic heart transplantation; PA, pulmonary artery; SCD, sudden cardiac death; VF, ventricular fibrillation.

in the same sinus of Valsalva. In other variations, the coronary origin may be high above the sinotubular junction or may have a common origin with the other coronary artery in the same sinus. In AAOLCA, the right sinus contains a normal-appearing right coronary ostium and usually a tiny slit-like ostium for the left coronary artery. In comparison, for an AAORCA, the left aortic

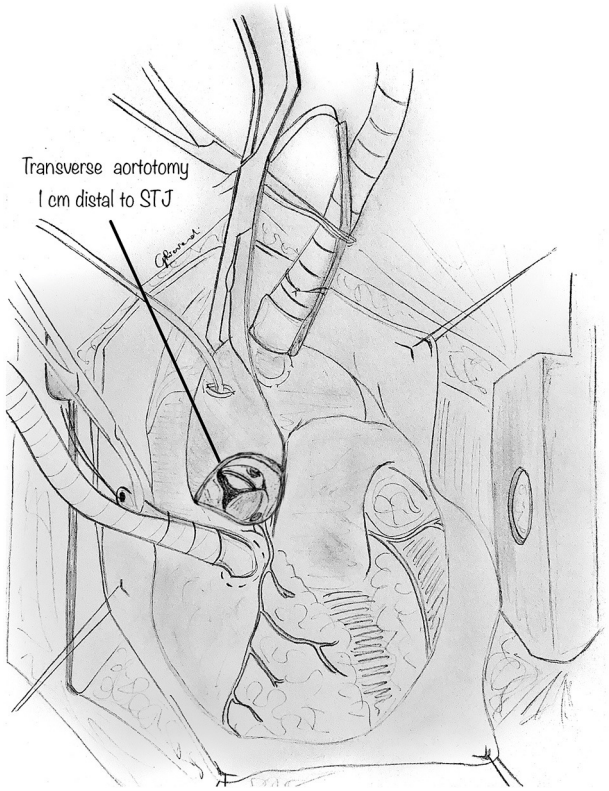

FIGURE 2 | Following a cardioplegic arrest of the heart, a transverse aortotomy is made above the sinotubular junction. The aortotomy is then extended parallel to the annulus of the aortic valve, directed to the left inter-coronary commissure. Additional care must be paid in case of high intramural course of proximal tract of the coronary, to avoid accidental lesions to the anomalous coronary.

sinus contains a normal-appearing left coronary ostium and a right coronary ostium which may similarly be abnormal.

The orifice of the anomalous coronary is gently explored with a coronary probe to define an eventual intramural segment's extent and its relationship to the correct sinus (**Figure 3A**). When the ostia have been identified within the aortic root, a small right-angle clamp can be gently placed into the anomalously located coronary ostium (**Figure 3B**), and a #15 blade can be safely used to unroof the overlying common wall of the coronary artery and aorta (**Figure 3C**), along with the intracoronary clamp. The incision may be refined with fine scissors. The target is to incise the common wall until the origin of the anomalous coronary artery from the aorta is exposed, and the coronary exits the aorta from its right sinus.

In some instances, the intramural portion of the coronary may go from one aortic sinus into the next by traversing the commissural plane, and it is not located entirely above the commissure (**Figure 4A**). In this situation, the typical unroofing procedure (with the incision of the entire length of the intramural portion) is contraindicated since it would damage the commissure and disrupt the aortic valve leaflets. Thus, the commissure is usually detached, and the intramural portion of the coronary is unroofed by cutting with fine scissors along its course until the coronary take-off from the aortic wall (**Figure 4B**). Lastly, the entire intramural course is unroofed, and the intima tacked around the new coronary ostium (**Figure 4C**). Last, the detached commissure is suspended above the unroofed intramural segment with pledgeted suture(s) (**Figure 5A**). Commissural resuspension is a technique that may lower the rate of aortic valve regurgitation and does not add any proven additional risk to the procedure (29). Alternatively, when the intramural coronary segment courses below the sino-tubular junction, a "neo-ostium" can be created in the correct sinus, at the point where the coronary artery emerges from the aortic wall (**Figure 5B**). This new ostium is enlarged further, and in this way, the coronary commissure is left intact, leaflet motion is not jeopardized, and a double coronary ostial communication is created. As a result, the angle of take-off of the coronary artery from the aorta is normalized.

After unroofing the intramural segment and creating a neo-ostium in the right sinus of Valsalva, interrupted tacking sutures (7-0 polypropylene) are placed circumferentially around the ostium to secure the coronary intima to the aortic wall to prevent intimal dissection at the neo-orifice (**Figure 5C**).

A novel unroofing technique has recently been described for adult patients, using electrical cautery to unroof the shared wall tissue along the coronary artery's intramural course (30). With this approach, the surgeon can directly follow the intramural tunnel path and evaporate the aortic wall roof without using a sharp blade to excise the roof of the tunnel. The authors believe that fulguration may be a more straightforward, faster, and better-controlled procedure that can also minimize the risk of potential flap dissection. Also, a wider excision of the shared wall and shorter aortic cross-clamp and cardiopulmonary bypass times are reported. However, a longer and larger follow-up is required to confirm this technique's safety, mainly regarding the potential for coronary endothelial damage that the use of thermal energy can cause.

In conclusion, the unroofing technique presents several advantages. It usually can relocate the functional orifice from the anomalous position to the appropriate sinus. Also, it can enlarge the orifice significantly and eliminate the portion of the vessel that lies between the great arteries. However, the more distal part of the intramural segment, at the point where the coronary artery leaves the aortic wall, is left intact, and the angle of take-off at times may only be minimally normalized. This area may occasionally remain severely stenotic. Thus, an acute take-off angle, the ostium's eccentricity, and hypoplasia of the initial coronary segment may not be adequately addressed by simple unroofing. Also, when detaching and then resuspending the commissure, the aortic valve regurgitation remains at risk. Last, the recent recognition of the intercoronary pillar is of some interest, a thickening of the aortic wall above the commissure, as a possible contributor to both pathophysiology of AAOCA and aortic valve support (29). The intercoronary pillar is the aortic wall segment above the intercoronary commissure, usually thicker than the remaining wall. Usually, the anomalous coronary artery travels from the incorrect sinus and behind and close

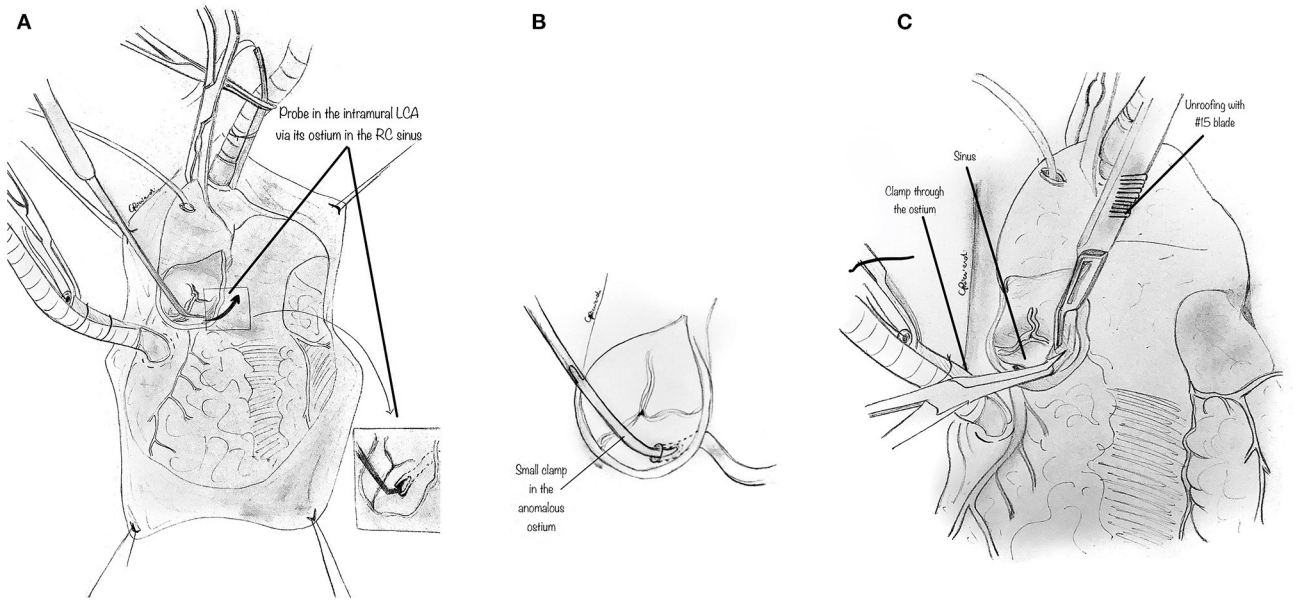

FIGURE 3 | Unroofing technique. **(A)** The orifice of the anomalous coronary artery origin is gently explored with a coronary probe to determine the extent of any intramural segment and its relationship to the correct sinus. **(B)** Diagram showing a small right-angle clamp which is gently placed into the anomalously located coronary ostium to determine its intramural course and evaluate the overlying common wall of the coronary artery and aorta. **(C)** Diagram showing a small right-angle clamp inserted into the anomalously located coronary ostium, and gently pushed inside the intramural course, to reveal the overlying common wall of the coronary artery and aorta which is incised with a blade and unroofed.

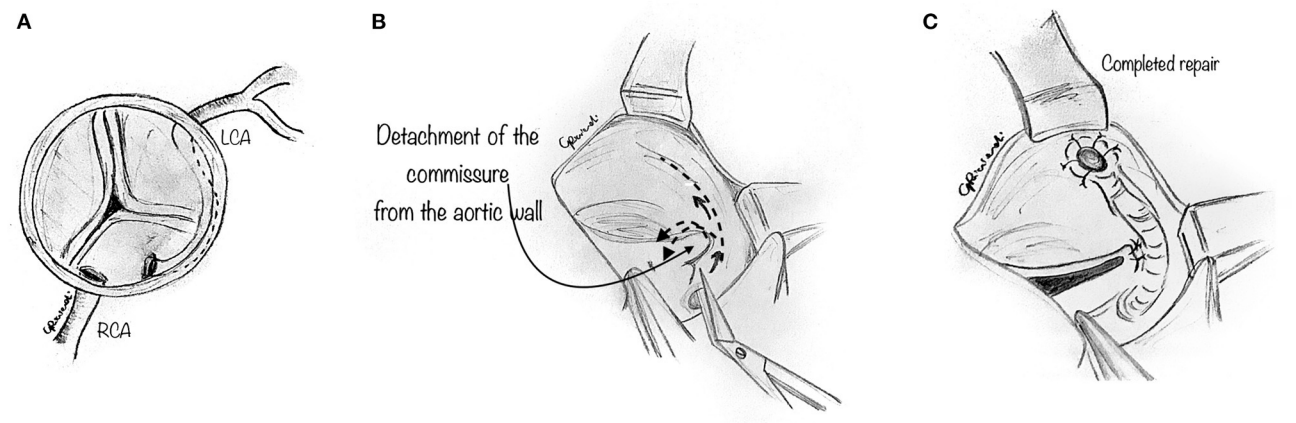

FIGURE 4 | Unroofing technique. The composite figures show a case of AAOLCA in which the intramural portion of the coronary goes from one aortic sinus into the next one by traversing the commissural plane **(A)**. The commissure is gently detached with a blade or fine scissor to expose the intramural portion of the coronary artery **(B)**. Then, the intramural portion of the anomalous coronary is unroofed, by cutting with fine scissors along its course until the take-off of the coronary from the aortic wall. Lastly, the entire intramural course is unroofed and the intima tacked around the new coronary ostium **(C)**.

to this thickened segment. While the unroofing of a long intramural segment can effectively move the ostium into the correct sinus and away from the intercoronary pillar when the intramural segment is short, the simple unroofing may be ineffective since the anomalous coronary artery may be left close to the pillar, and at risk for potential compression. Some authors have reported (29) that the latter can occur after unroofing and suggest alternative surgical techniques in such cases, i.e., coronary translocation. Furthermore, this potential negative outcome may be even more probable when the coronary commissure needs to be resuspended after unroofing of a short segment since this can replace the inter- coronary pillar close to the new coronary ostium.

Ostioplasty Techniques

An alternative technique for AAOCA with ostial stenosis and the intramural course is extensive coronary ostioplasty, also called "anatomical surgical repair." As reported by Vouhè et al. (27, 31),

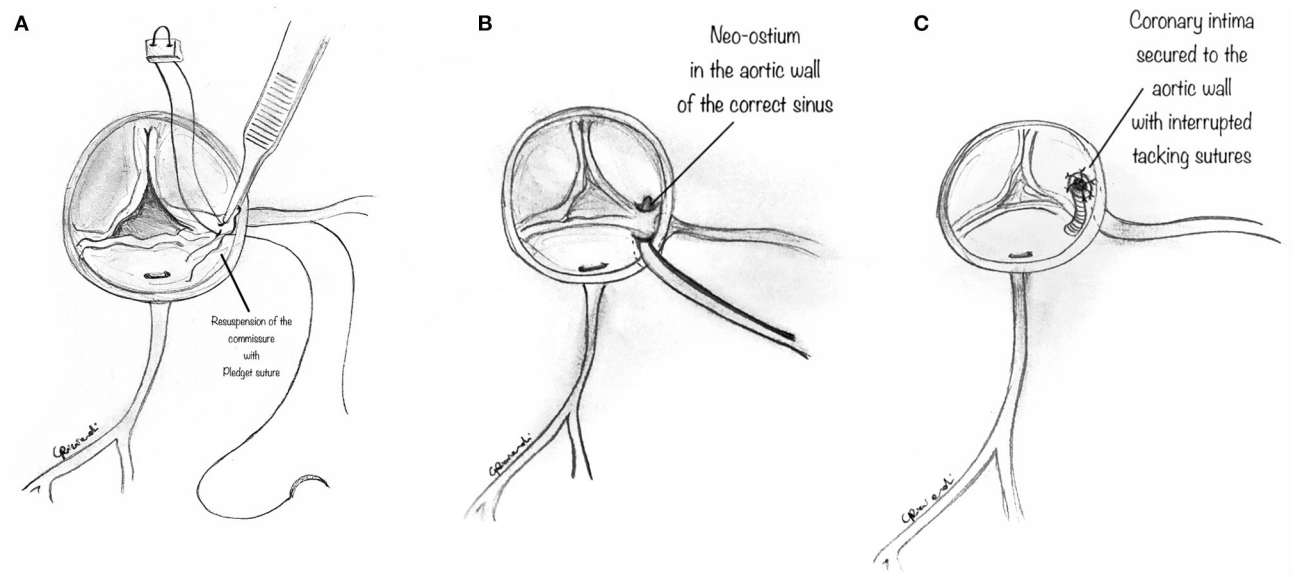

FIGURE 5 | (A) The diagram shows that the previously detached commissure is then resuspended with pledgeted sutures in order to create a neo-commissure, and preserve aortic valve integrity. **(B)** The diagram shows a surgical alternative when the intramural coronary segment is located below the commissure. In such a case, a "neo-ostium" can be created in the aortic wall of the correct sinus, opposite to the point where the coronary artery emerges from the aortic wall. **(C)** Interrupted tacking stitches are placed circumferentially around the ostium, securing the coronary intima to the aortic wall with the aim of preventing intimal dissection at the neo-orifice.

the anomalous coronary ostium is completely reconstructed by two incisions, one in the aortic sinus and the other longitudinally on the initial epicardial course of the anomalous coronary artery, which are then joined together.

In detail, the aortic and pulmonary roots are separated (**Figure 6A**) from each other down to the annular level to expose the epicardial course of the anomalous coronary artery. This step may be facilitated by the division of the PA trunk (31). The normal epicardial course of the left coronary artery is identified and exposed by removing all surrounding connective tissue. Then, the aorta is transected at the sinotubular junction (**Figure 6B**). The initial epicardial course of the anomalous (left or right) coronary artery is incised longitudinally (**Figure 6C**). The ascending aorta is incised vertically in the left coronary sinus toward the coronary incision, beginning from the aorta's cut edge. The two incisions, aortic and coronary, are joined at the point where the coronary artery leaves its intramural course to become epicardial (**Figure 6D**). The intramural segment of the coronary artery is thus left intact but essentially bypassed. Then, a patch of prosthetic material, usually pericardium (although the best patch material to use is yet to be determined), is implanted onto the aortocoronary incision to create a large coronary neo-ostium in the correct aortic sinus. Then, the ascending aorta is reconstructed, incorporating the coronary patch into the anastomotic suture line. Whenever the pulmonary trunk has been transected, it is advisable to reconstruct it after extensive mobilization of the pulmonary arteries. Extreme care must be taken to rule out any residual compression of the reconstructed coronary artery by the PA. Usually, the division of the main PA is not required for AAORCA.

When associated with unroofing, the anatomical repair may be realized with a single incision starting from the cut edge of the ascending aorta, vertically in the coronary sinus, and easily extended in the epicardial course of the coronary artery, which is incised longitudinally.

Anatomical repair with ostioplasty addresses several components of AAOCA: the neo-ostium is enlarged with the patch in the appropriate sinus, with a repair that essentially circumvents the abnormal intramural segment and creates a larger neo-ostium in the appropriate sinus, just at the end of the intramural segment. Doing this, the commissure is left intact, and the risk of iatrogenic aortic insufficiency (due to commissure takedown) may be minimized. According to Vouhè et al. (27, 31), this technique may be effective in most anatomical variants with or without an intramural course, except those with an acute take-off angle or commissural ostial location. The reported early and mid-term results are satisfactory, although the long-term outcomes are still unknown. However, it is a more technically demanding procedure, with a patch in the coronary course, which may thrombose in the long term (27).

One question that remains is which patch material is best. Vouhè et al. (27) suggest a pericardial patch, preferably. However, long-term results are needed to verify what is best. Progressive aneurysmal dilatation of the coronary patch was reported when a saphenous vein patch was utilized, and reoperation was required. An autologous pericardial patch may avoid this complication, as derived from experience with coronary angioplasty in the setting of intramural coronaries in transposition of the great arteries or left main coronary artery atherosclerosis. However, long-term outcomes remain uncertain. Lastly, the potential for late calcification of a pericardial patch, which enlarges the coronary

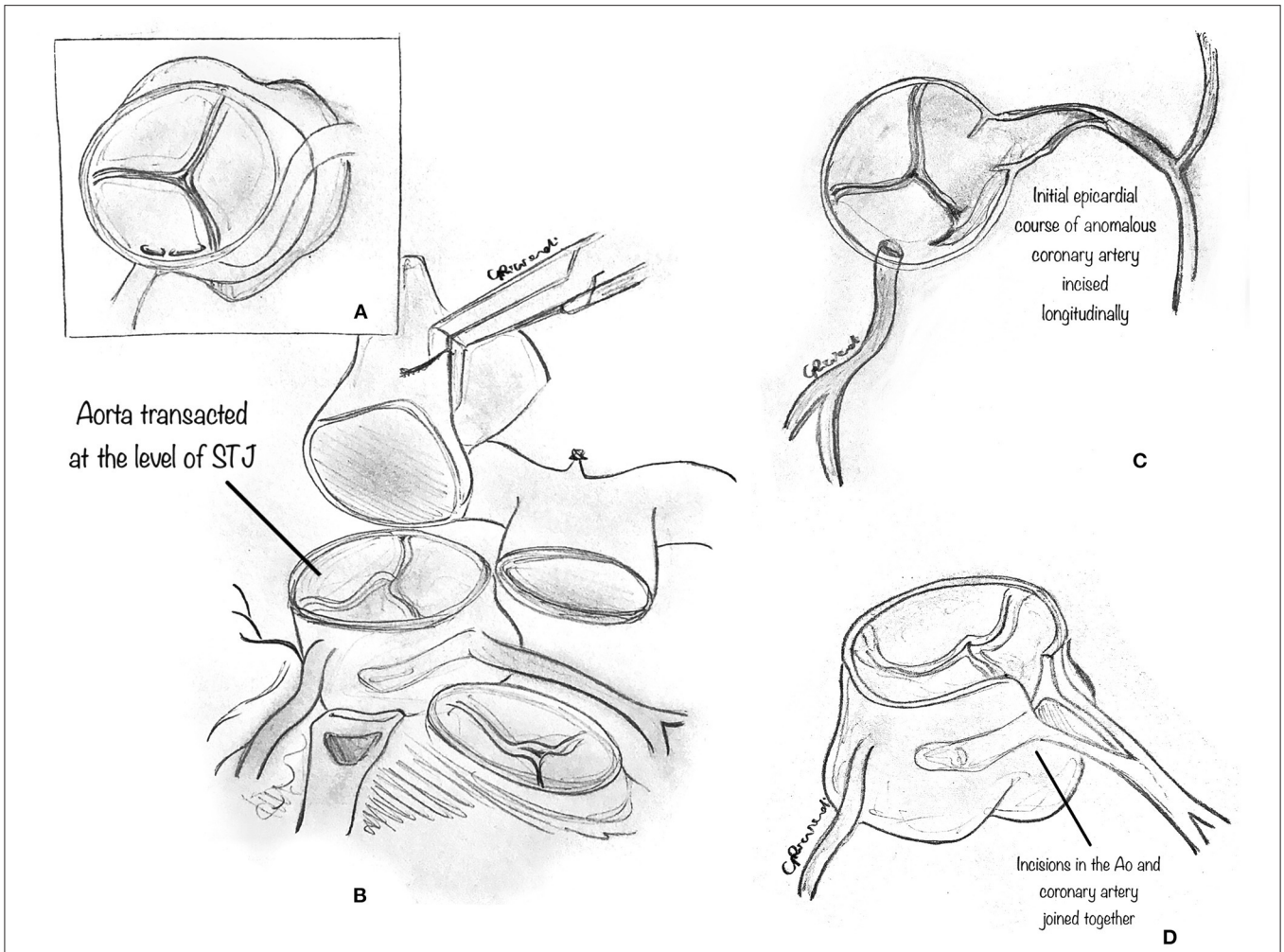

FIGURE 6 | Ostioplasty technique. **(A)** The diagram shows that the aortic and pulmonary roots are separated from each other down to the annular level, to expose the epicardial course of the anomalous coronary artery. **(B)** The normal epicardial course of the left coronary artery is identified and exposed by removing all surrounding connective tissue. The aorta is transected above the sinotubular junction. **(C)** The proximal epicardial course of the anomalous left coronary artery is incised longitudinally. **(D)** The ascending aorta is incised vertically in the left coronary sinus toward the coronary incision, beginning from the cut edge of the aorta. The two incisions, aortic and coronary, are joined at the point where the coronary artery leaves its intramural course to become epicardial.

ostium, exists. The use of a prosthetic patch on a coronary artery or ostia is a matter of concern for long-term outcomes. Further and longer follow-up is needed to confirm the safety and long-term effectiveness of this technique.

Reimplantation

The reimplantation technique is usually reserved for those cases where the anomalous coronary artery course is not intramural, and the coronary arteries have separate origins, or when the commissure is close to the anomalous segment (24, 32). After the usual initial surgical steps, the aberrant coronary artery is identified, dissected free along its course, and mobilized, as commonly performed for an arterial switch operation with a low setting on the cautery. As described above, a transverse aortotomy is performed to better visualize the anomalous coronary artery (**Figure 7A**). The aortic sinuses are carefully inspected to identify an eccentric location in the sinus, a proximal intramural portion, or a slit-like orifice. Attention must be paid to avoid damage to the other coronary ostium, which may be very close. A button of tissue around the ostium of the coronary artery is excised, as in the arterial switch operation (**Figure 7B**). A corresponding portion of the correct sinus is then incised either with an aortic punch (**Figure 7C**) or through a medial trap-door technique (**Figure 8A**), according to the surgeon's preference. Extreme care is taken to avoid any tension or unnatural kinking of the anomalous coronary artery. The reimplanted coronary position is usually above the correct coronary sinus, distal to the sinotubular junction, to move the coronary artery away from its interarterial course and eliminate the potential for external compression. The coronary button is sutured with 6-0 to 7.0 prolene suture, according to the patient's body weight and surgeon's preference (**Figure 8B**). The ostium's original location is usually closed with a small prosthetic patch to reconstruct the aortic wall (**Figure 8C**). Finally, the aortotomy is closed in an

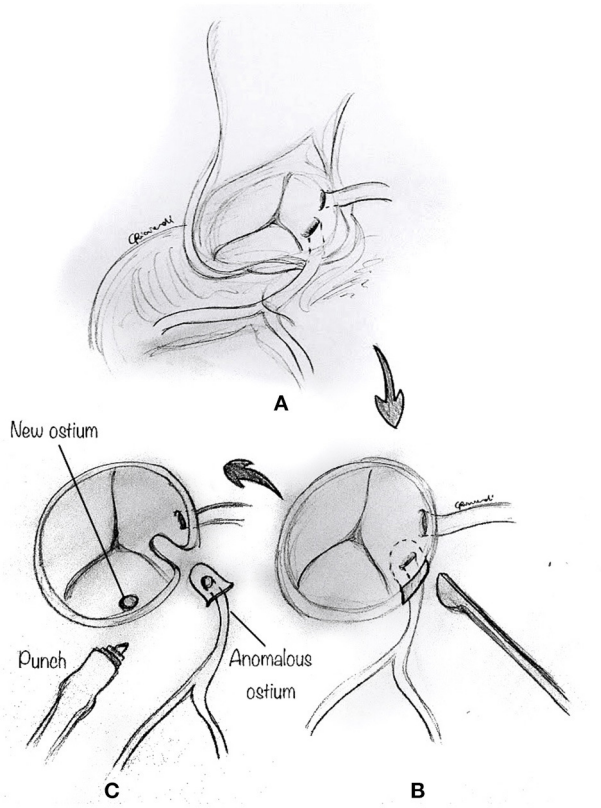

FIGURE 7 | Reimplantation technique. **(A)** The aberrant coronary artery is identified, dissected free along its course, and mobilized by means of low cautery. **(B)** A button of tissue around the ostium of the coronary artery is excised. Attention must be paid to avoid damage to the other coronary ostium, which may be very close. **(C)** A corresponding portion of the correct sinus is then incised with an aortic punch.

end-to-end fashion, with or without reinforcement of the suture line. When the coronary ostium is very close to the commissure, some authors have reported a successful alternative technique in adult patients, consisting of the transection of the anomalous coronary artery at the external aortic exit site, without a button. Then they proceeded to do an end-to-side anastomosis (32).

Selecting the ideal site for reimplantation is crucial in this technique. Coronary reimplantation requires extended coronary mobilization and a perfect repositioning of the coronary in the appropriate sinus to avoid kinking or distortion. When the reimplantation site is too low (whose recognition usually occurs after the bypass is weaned), with suitable ostial enlargement, one can resect a small anterior portion of the aorta above the anastomosis to relocate the right ostium (31) indirectly. This allows adjustment of the effective reimplantation height without the need for resuturing the entire coronary anastomosis.

Pulmonary Artery Translocation

An alternative approach to AAOCA repair is to translocate the PA away from the aorta, leaving the coronary vessels undisturbed. The principle of the PA translocation (anterior or lateral) is to move the PA away from the aorta and create additional space between the great arteries, reducing the risk of compression of the anomalous coronary artery as it courses between them. This has been demonstrated quite clearly in the postoperative CTA images by Guerra et al. (33), who report an increase in the distance between the PA and the shared virtual origin of the coronaries of about 5 mm. The main advantage of this procedure is that it can be performed without cross-clamping, i.e., on a beating heart.

Technically, the perivascular soft tissue between the aorta and the PA is debulked. The distal main PA is transected at the bifurcation (**Figure 9A**), and the left PA is incised toward the left hilum (**Figure 9B**). A patch of prosthetic material (pulmonary homograft or pericardium) is sutured to enlarge the PA confluence opening and prevent right PA stenosis (**Figure 9C**). The main PA is then re-anastomosed toward the left hilum, resulting in a widely patent main PA and pulmonary branches (**Figure 9D**).

Since this technique does not correct the potential causes of coronary hypoperfusion (i.e., slit-like ostium or stenotic intramural segment), we believe it should be utilized in those patients in whom alternatives techniques should be avoided, such as single coronary artery and main coronary artery coursing between the great arteries without an intramural course. Whether this maneuver will eliminate the risk of future coronary compression is not sure since the mechanisms of ischemia in AAOCA go beyond inter-arterial compression. However, PA translocation has some significant advantages: it can be performed on a beating-heart, avoiding myocardial ischemia, and minimal risk of bleeding because of lower PA pressure. As reported and advocated for elsewhere (15), PA translocation is primarily performed as an additional low-risk procedure to other more invasive techniques, such as unroofing or ostioplasty.

Coronary Artery Bypass Graft (CABG)

This traditional technique is performed in the usual fashion (**Figure 10**). CABG alone may be best suited when other procedures are contraindicated, such as in AAOCA with severe proximal narrowing or in older patients with diffuse atherosclerosis (15, 26), where it shows good early and midterm results. However, CABG, usually with an internal mammary artery bypass, is not recommended in young patients. Since the flow through the anomalous coronary artery is minimally restricted at rest, the mammary bypass may have decreased patency secondary to competitive flow. Fedoruk et al. (34) described 40% late graft occlusion in 5 patients with AAORCA treated with right internal mammary artery graft, while Tavaf-Motamen et al. (35) reported two patients treated with CABG for AAORCA, both of whom had early graft failure with recurrence of symptoms and graft failure. Thus, ligation of the coronary artery proximal to the graft's insertion is an essential step to CABG's success in this setting.

DISCUSSION

As outlined above, several techniques have been reported to repair AAOCA, but they are heterogeneous and difficult to compare in their effectiveness as different techniques

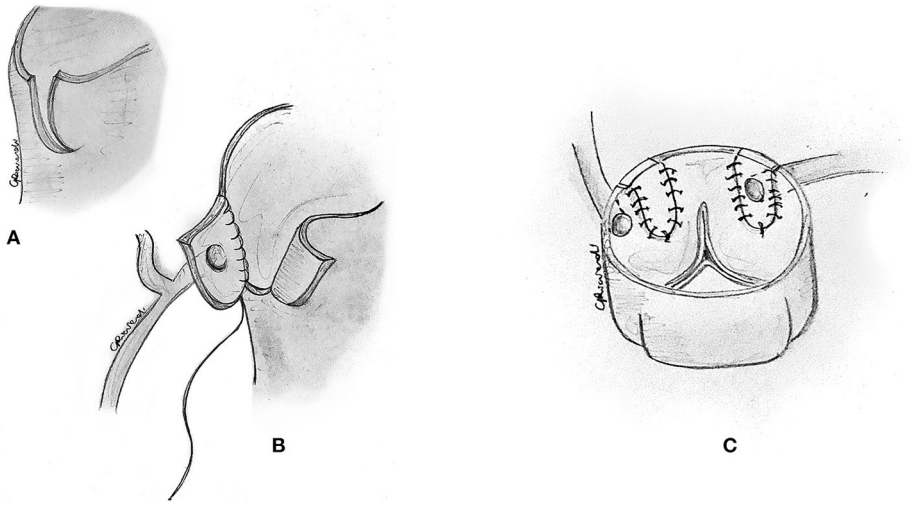

FIGURE 8 | Reimplantation technique. **(A)** Alternatively, a corresponding portion of the correct sinus is incised through a medial trap-door technique. **(B)** The coronary button is sutured to the aorta in its new position. **(C)** The original location of the ostium is usually closed with a small prosthetic patch to reconstruct the aortic wall.

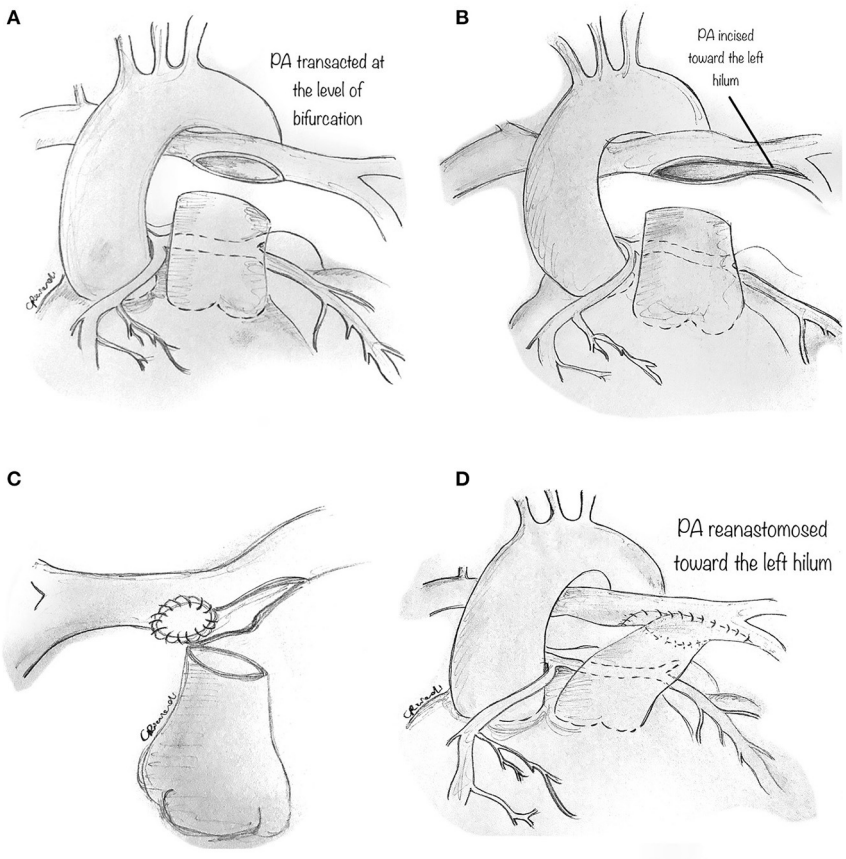

FIGURE 9 | Pulmonary artery translocation technique. **(A)** The perivascular soft tissue between the aorta and the pulmonary artery is debulked. The distal main pulmonary artery is carefully transected at the bifurcation. **(B)** The left pulmonary artery (PA) is incised toward the left hilum. **(C)** A prosthetic material (pulmonary homograft or heterologous pericardium) is then fashioned to widely patch the opening in the PA confluence so as to avoid right PA stenosis. **(D)** The main PA is then re-anastomosed toward the left hilum, resulting in a widely patent PA and pulmonary branches.

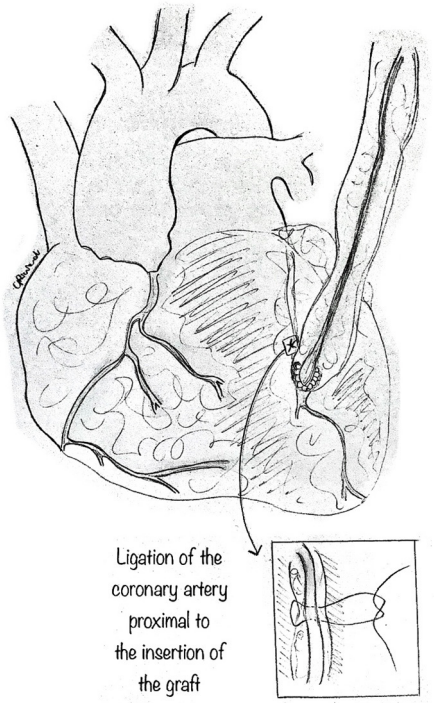

FIGURE 10 | Coronary artery bypass graft. The standard technique can be used, especially in older patients, utilizing the mammary artery as graft to the coronary. In such a case, it is imperative to ligate the coronary artery tract proximal to the insertion of the graft, so as to avoid competitive blood flow which may cause graft.

are required based on the different anatomical variations. Besides, indications for surgery are still controversial. While most surgeons still favor repair of AAOLCA even if asymptomatic, repair of asymptomatic AAORCA remains highly controversial (20, 36, 37).

The various surgical techniques are usually devoted to a particular anatomical subtype of coronary anomaly and only deal with 1 or 2 pathophysiological mechanisms of hypoperfusion (5). Ideally, the coronary surgical reconstruction for AAOCA should normalize the anatomy, relocating a large ostium in the center of the appropriate sinus, reproducing a normal take-off angle, and eliminating any intramural or interarterial course. As a matter of fact, none of the techniques described above can address all of these components, and each is susceptible to individual technical pitfalls. Also, the use of a prosthetic patch on a coronary artery or ostia is a matter of concern for long-term outcomes.

To summarize, the following techniques should be considered as the repair for these specific issues.

Unroofing is indicated to manage an intramural course. However, it can be limited by the commissure location, leading to the requirement for a commissural resuspension. Ostioplasty is primarily utilized to manage a small or stenotic coronary origin. The anatomical repair technique (31) and the recently described "unflooring" technique (that includes a patch augmentation of the intramural course in addition to standard unroofing) (38) imply an increasing technical effort aimed at optimizing the clinical outcomes. While it eliminates the inter-arterial course and the entire intramural segment and augments the coronary ostium by a pericardial patch plasty, a limitation of this procedure is that the exit from the aorta is very eccentric, typically with a very acute take-off angle that may be difficult to correct.

Furthermore, a prosthetic patch is utilized, with the potential of possible late ostial stenosis. Coronary reimplantation is to be favored when the intramural segment is too short or absent, and adjunct PA is used to increase the space around the coronary artery potentially. Last, PA translocation may be preferentially utilized as an additional low-risk procedure in an attempt to improve the outcomes. As such, a mixture of different surgical alternatives can be utilized to better repair AAOCA.

CONCLUSIONS

A thorough understanding of coronary pathology and applying the appropriate operative techniques are critical to achieving excellent results for both adult and pediatric patients. A potential trend toward minimally invasive approaches to the surgical repair of AAOCA may be promising and could further improve quality of life. Investigations of long-term outcomes and a more comprehensive understanding of this lesion's natural history and its variations remain imperative.

AUTHOR CONTRIBUTIONS

MP conceptualized, wrote, and revised the paper, coordinated the team, and supervised the authors. AJ and AG conceptualized and revised the paper. DB revised literature and revised the paper. GR revised the paper and produced the artwork. All authors contributed to the article and approved the submitted version.

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Coronary Arteries: Normal Anatomy With Historical Notes and Embryology of Main Stems

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Anatomy of subepicardial coronary arteries became a topic of investigation at autopsy in Florence (Italy) by Banchi in the early twentieth century, with the discovery of dominant and balanced patterns. Thereafter, in the 60's of the same century Baroldi in Milan did post-mortem injection with spectacular three-dimensional casts. Later Sones at the Cleveland Clinic introduced selective coronary arteriography for *in vivo* visualization of coronary arteries. In the present chapter we show these patterns, as well as normal variants of origin and course with questionable risk of ischemia, like myocardial bridge as well as origin of the left circumflex coronary artery from the right sinus with retroaortic course. As far as embryology, the coronary arteries and veins are epicardial in origin and finally connect the former with the aorta, and the latter with the sinus venosus. At the time of spongy myocardium, intramural blood supply derives directly by the ventricular cavities, whereas later, at the time of myocardial compaction, vascularization originates from the subepicardial network. The connection of the subepicardial plexus with the aorta occurs with prongs of the peritruncal ring, which penetrate the facing aortic sinuses. Septation of truncus arteriosus is not responsible for the final position of the coronary orifices. Infact in transposition of the great arteries coronary ostia are regularly located within facing sinuses of the anterior aorta.

Keywords: embriology, anatomy, coronary arteries, history, normal variants

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INTRODUCTION

This chapter on anatomy and embryology of coronary arteries (CAs) has been written having in mind that the target readers are clinicians. Explaining embryology is a difficult task, and we did our best to simplify the message and facilitate the comprehension. Coronary arteries anomalies and their clinical implications are the argument of another chapter from our group for this e-book.

Moreover, it has been our deliberate intention to cover some history of CA anatomy, with relevant illustrations, to enhance the interest of the readers.

HISTORICAL NOTES

The pathology of CAs started to be a topic of interest and investigation at the beginning of the twentieth century, when myocardial infarction was found to be related to coronary obstruction. Even Morgagni in his book, dated 1761, skipped the issue (1).

Antonio Banchi, an anatomist in Florence, in 1903 first published a milestone paper, written in Italian, on subepicardial CAs in normal hearts and introduced the concept of right and left

dominance as well as balanced coronary circulation (2), according to the CA supply of the posterior wall of the left ventricle (**Figure 1**).

These anatomical patterns of the coronary arterial system were confirmed through postmortem injection and casts by Giorgio Baroldi in 1963 (**Figure 2**) (3). The plastic substances were "Geon Latex 576" and "Neoprene 842A." These substances, which are fluid at room temperature, solidify at 40–50°C. They were injected into the aorta under pressure, ranging from 130 to 200 mmHg, maintained for a 5- to 10-min period.

With the latex maintained under pressure, it was solidified by placing the heart in 10% formalin at 40–50°C from 48 to 72 h. Following solidification of the latex, the heart was allowed to further fix in a new 10% formalin solution at room temperature for a period of 12–48 h. Finally, the injected and fixed heart was digested in a concentrated hydrochloric acid solution.

The invention and clinical diagnostic application of selective coronary arteriography by Sones at the Cleveland Clinic (4) permitted to identify these arterial patterns *in vivo*, as a requisite for bypass surgery.

ANATOMY OF CORONARY ARTERIES

The CAs take origin from the sinus portion of the aortic root, with the orifices located usually at the sino-tubular junction, with a variability of up to 2.5 mm (5) (**Figures 3**, **4**). The left coronary ostium is located in the left anterior aortic sinus and the right coronary ostium in the right anterior aortic sinus, namely, the aortic sinuses facing the pulmonary artery (6) (**Figure 5**). Right and left CAs originate perpendicularly from the aorta, and their proximal course is not hindered by the pulmonary trunk (**Figure 5**). Usually, a single orifice is located in the left aortic sinus, giving origin to the left main trunk, which divides into anterior descending and left circumflex coronary branches (**Figures 2a**, **5**). The course of the former occurs over the interventricular septum while the latter in the left atrioventricular (av) groove, with different lengths according to the dominant pattern. An intermediate artery may originate in between the two, so that the left main stem trifurcates. From the left anterior descending CA, diagonal lateral arteries take origin, for the blood supply of antero-lateral free wall of the left ventricle (**Figure 2a**), and perforating arteries,

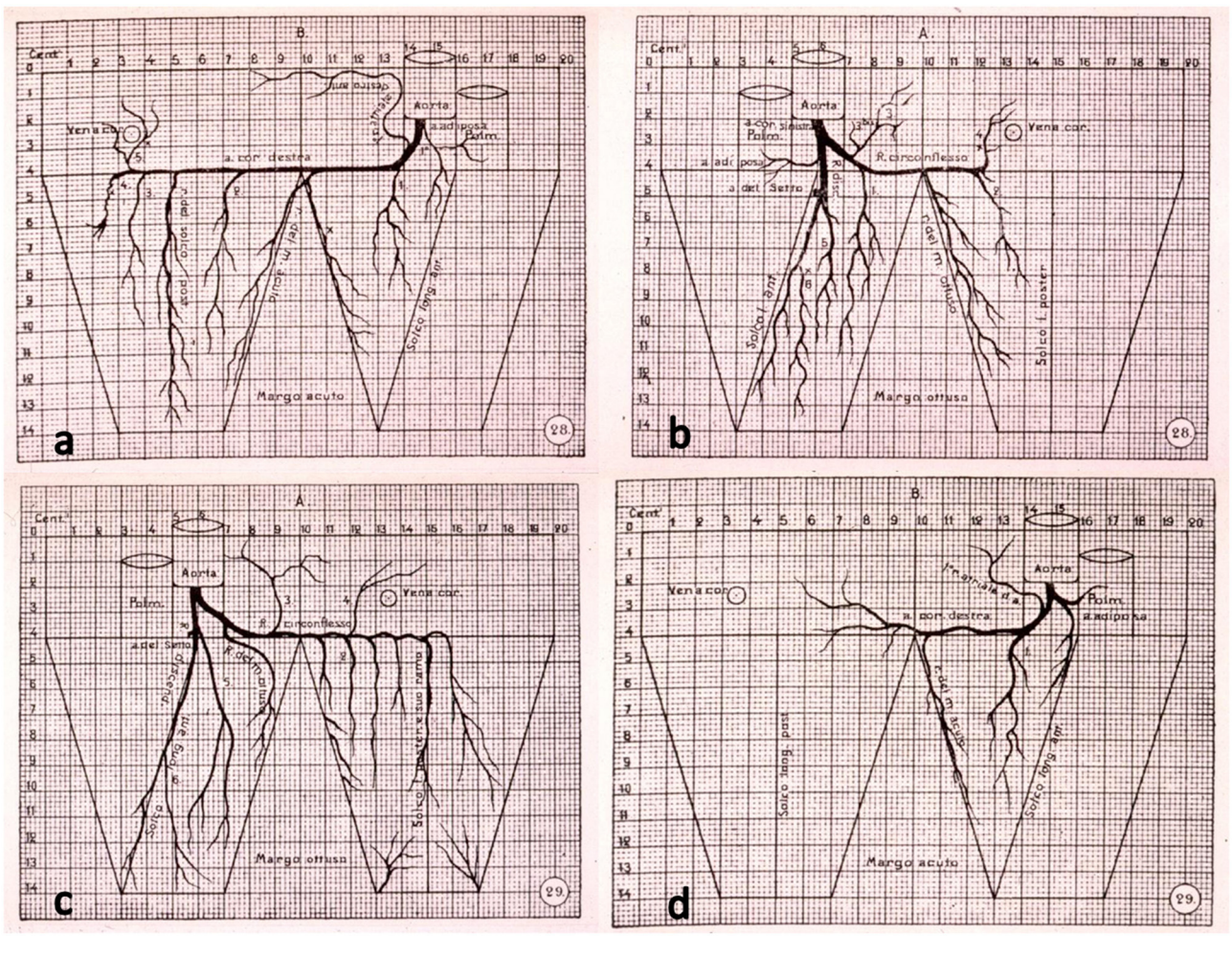

FIGURE 1 | The original drawings of coronary artery dominant patterns, from Banchi (2). **(a,b)** Right dominance and **(c,d)** left dominance.

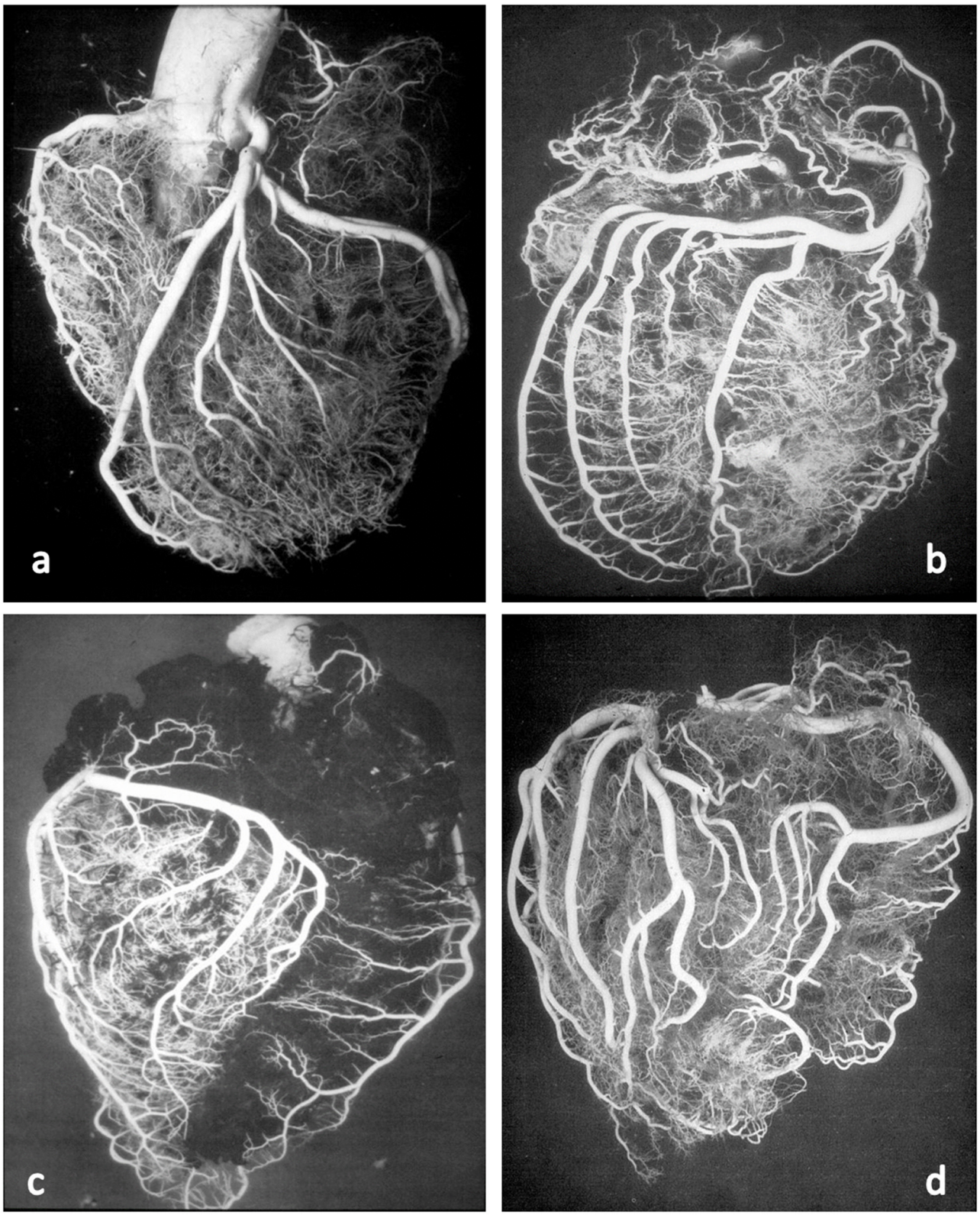

FIGURE 2 | Postmortem casts of coronary arteries. From Baroldi and Scomazzoni (3). **(a)** Left coronary artery anatomy, **(b)** dominant right pattern, **(c)** dominant left pattern, and **(d)** balanced pattern.

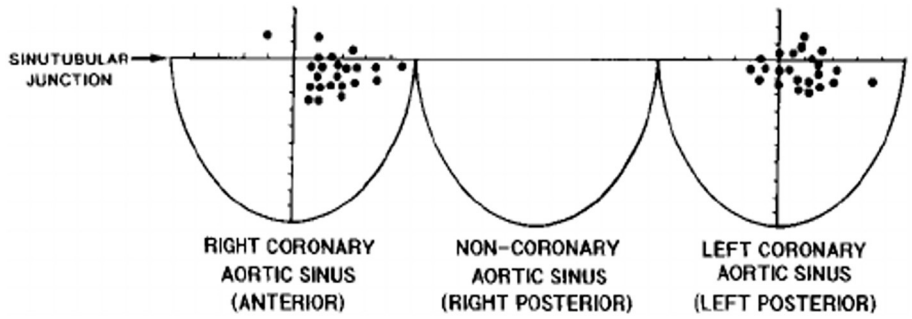

FIGURE 3 | The topographical variability of coronary artery orifices in normal hearts. From Muriago et al. (5).

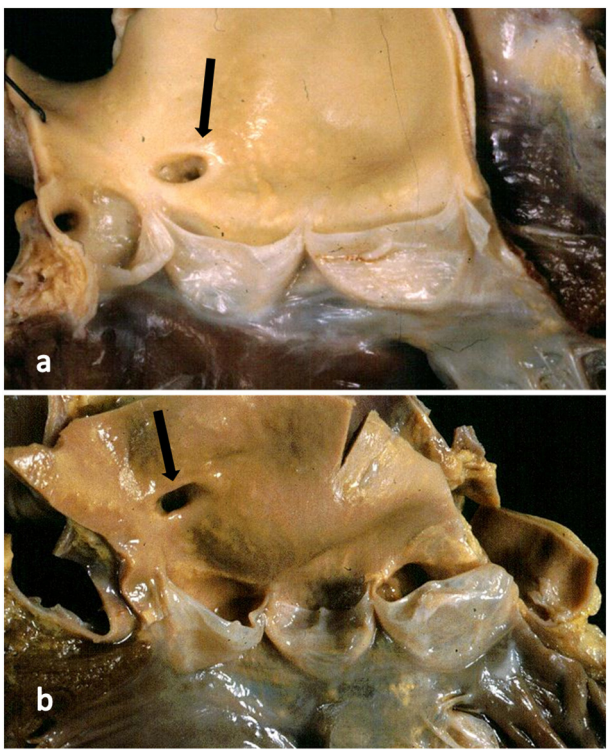

FIGURE 4 | (a) The right coronary artery orifice (arrow) is just above (2 mm) the sinotubular junction, within normal limits. **(b)** The right coronary orifice (arrow) is well above the sinotubular junction (10 mm), over the threshold of normal limits.

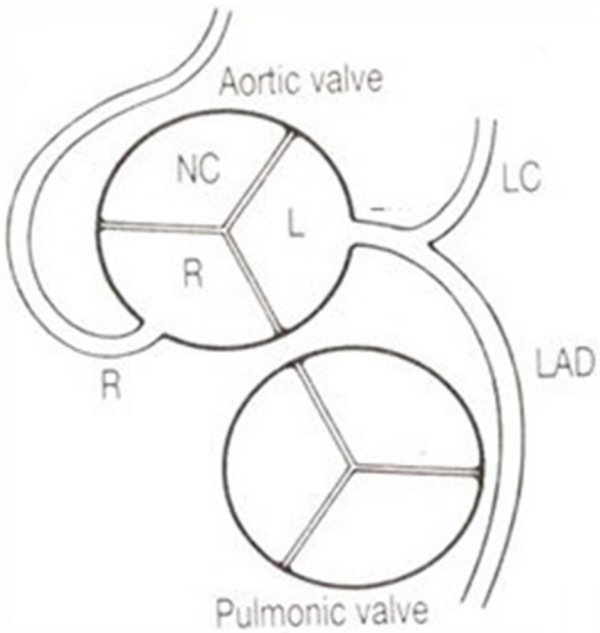

FIGURE 5 | The coronary arteries arise from the facing aortic sinuses, perpendicular to the aortic wall, and the pulmonary root does not interfere with their proximal course. Note the left stem dividing into the left anterior descending (LAD) and the left circumflex (LC) branches. From Roberts (6).

for the blood supply of two-thirds of the anterior ventricular septum (**Figure 6**).

A normal variant is the double descending CA (**Figure 7**), the interventricular one originating septal arteries and the other one diagonal branches.

From the left circumflex artery, the obtuse angle branch takes origin to supply the left lateral wall. It may represent the end of the left circumflex artery, in case of extremely dominant right CA.

According to Baroldi (3), a right dominant pattern is present in 79% of cases, left dominant in 7% and balanced in 14%. In two-thirds of the cases, the left anterior descending CA turns at the apex and runs in the posterior interventricular groove, even up to the crux cordis.

The left circumflex artery may originate from a separate orifice of the left aortic sinus, a condition considered a normal variant since it does not imply myocardial ischemia.

The same occurs to the right CA, since a conus artery almost regularly arises from a separate, anteriorly located small orifice. The right CA runs in the right av groove and reaches the crux cordis in a right dominant pattern, giving origin to the descending CA (**Figures 1a**, **2b**) to take over

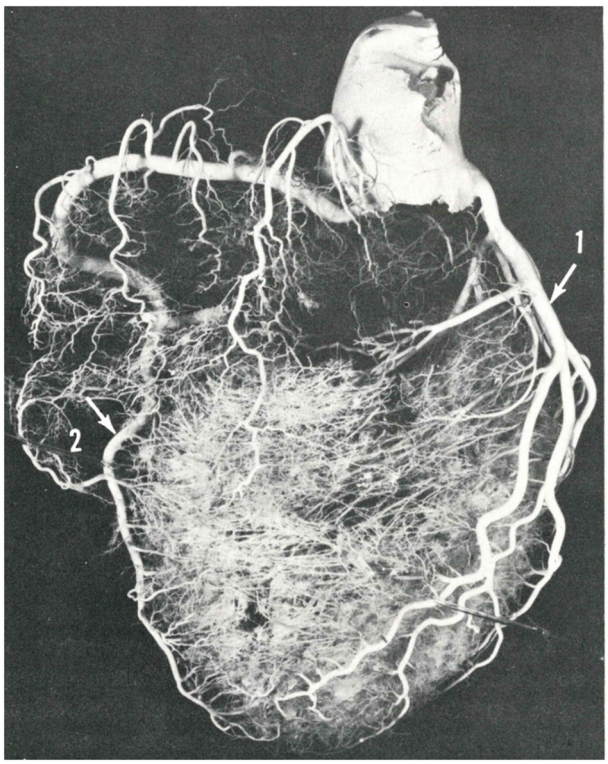

FIGURE 6 | The blood flow of the ventricular septum is supported by perforating branches, originating from the anterior and posterior descending coronary arteries. From Baroldi and Scomazzoni (3).

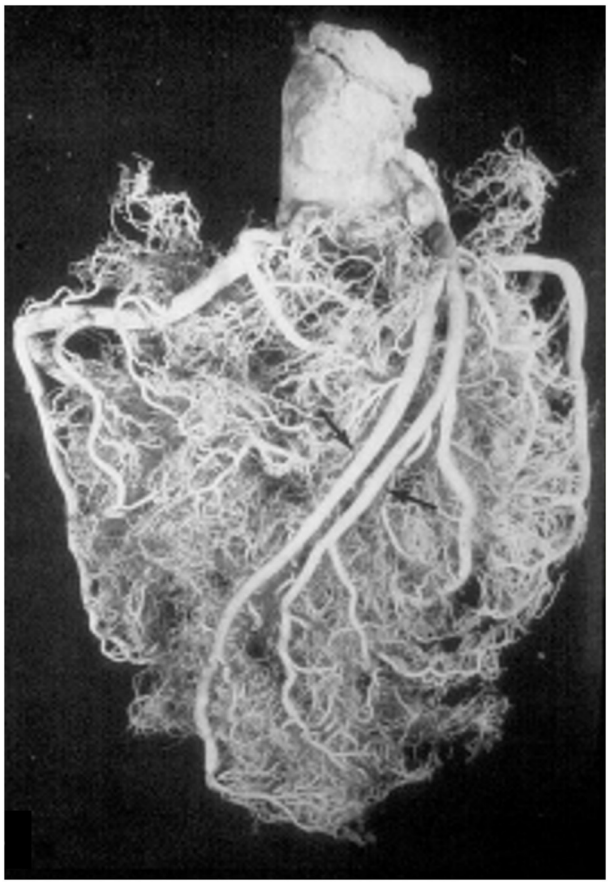

FIGURE 7 | A double left anterior descending coronary artery (arrows). From Baroldi and Scomazzoni (3).

the blood supply of the posterior third of the ventricular septum. It continues in the posterior left av sulcus, originating branches for the blood supply of the posterior left ventricular free wall.

Branches for the conduction system take origin from the dominant right CA, proximally the sinoatrial node artery and distally the av node artery from the crux cordis. In the setting of left dominant CA, both of these two small arteries originate from the left circumflex artery.

Another quite intriguing condition is the origin of the left circumflex artery from the right CA or from the right anterior aortic sinus itself, with a retroaortic course before reaching the left av sulcus (**Figure 8**). It has been observed in cases of sudden death as infarct-related artery in a postero-lateral myocardial infarction in the absence of any other explanation (7).

Nearly 30% of the population shows an intramural course of the proximal left descending CA (8–11) (**Figure 9**). It is considered a variant of normal when just covered by a myocardial bridge. It may be a cause of myocardial ischemia if completely surrounded by a sleeve of the myocardium with disarray and an intramyocardial course at least 2.5 cm long and 0.5 cm deep (9–11) (**Figure 10**). The condition is particularly at risk when the intramyocardial course is just over the first septal perforating artery (**Figure 6**).

The origin of the left anterior descending CA from the proximal right CA is also another normal variant, since it does not entail myocardial ischemia (**Figure 11**). However, the surgeon should be well aware of this unpredictable course while repairing conotruncal congenital heart diseases with a transannular patch or conduit implant.

The major subepicardial CAs are of medium size and, as such, with a "muscular" tunica media. After birth, a myointimal layer develops with time, due to migration of smooth muscle cells from the tunica media (12).

EMBRYOLOGY OF CORONARY STEMS

Both subepicardial CAs and veins are extracardiac in origin, deriving from epicardial cells (13, 14).

Their development begins with the formation of a plexus-like vasculature located in the subepicardium, which invades the myocardium and develops small vessels and capillaries.

Earlier, the myocardial blood supply derives directly from the ventricular cavities through the intertrabecular

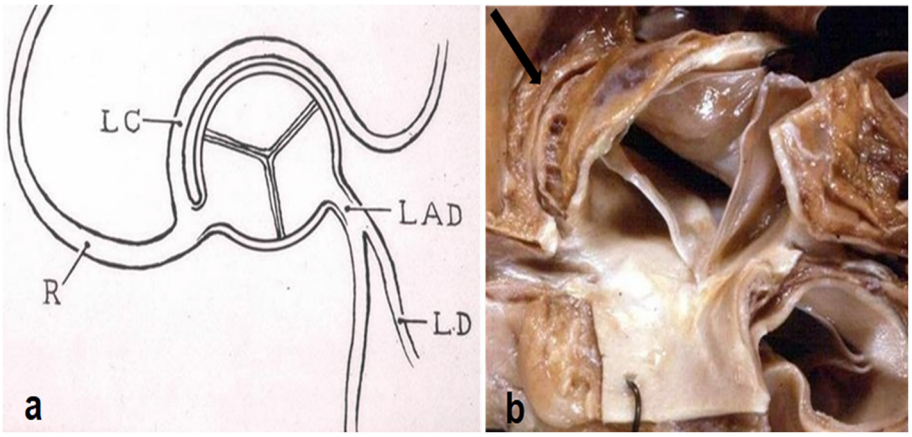

FIGURE 8 | (a) Diagram with origin of the left circumflex artery from the right coronary artery and retroaortic course. From Roberts (6). **(b)** Gross view of the aortic root. Arrow indicates the retroaortic course of the anomalous left circumflex artery.

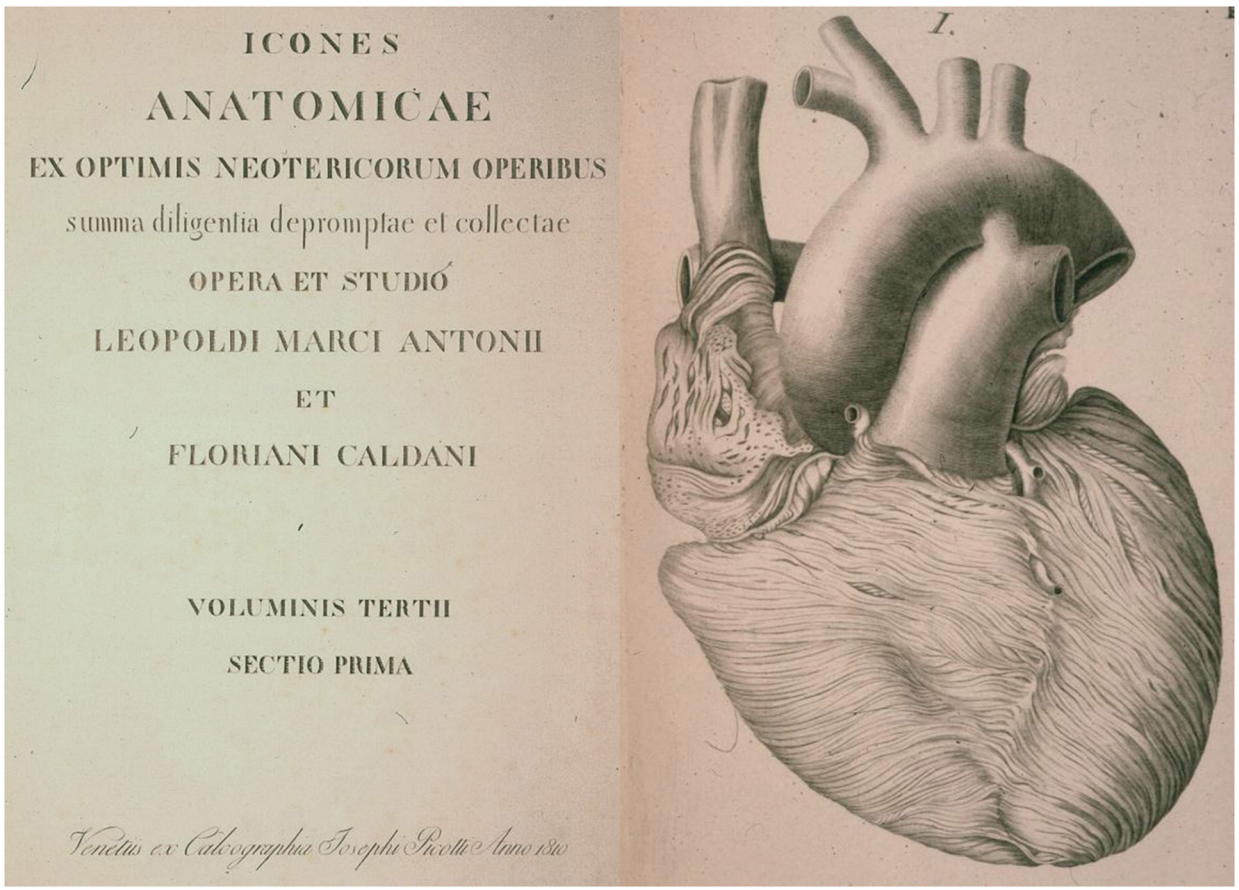

FIGURE 9 | The first historical description of myocardial bridge made in 1834 by Leopoldo and Floriano Caldani, Professors of Anatomy at the University of Padua. From Caldani et al. (8).

spaces lined by the endocardium (**Figure 12a**). This source of blood to the primitive spongy myocardium disappears with the myocardial compaction (**Figure 12b**). At this point, the whole intramyocardial vascularization consists of vessels with the endothelium derived from the subepicardium (14–16).

The origin of CAs and veins, whether intra- or extramural, is similar. Their definitive identity and function depend upon

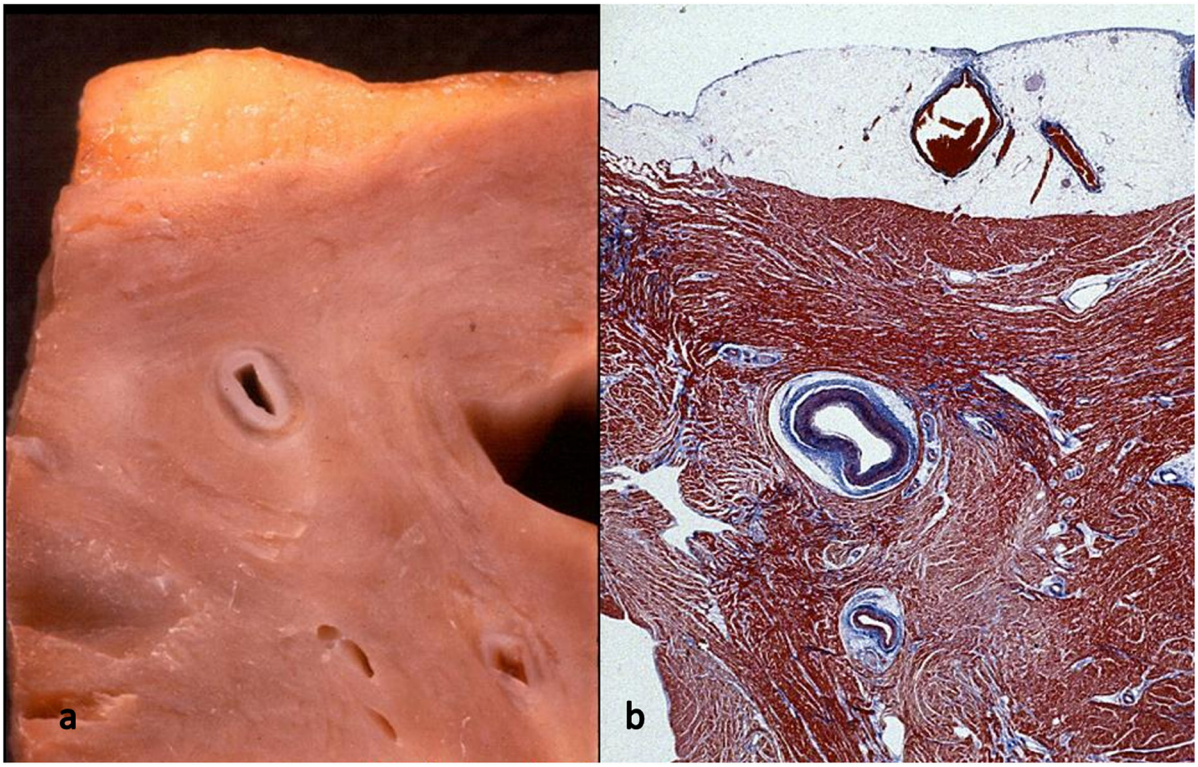

FIGURE 10 | Myocardial bridge with deep intramural course: the coronary segment is completely surrounded by a myocardial sleeve. Gross **(a)** and histological views **(b)**. Azan Mallory stain.

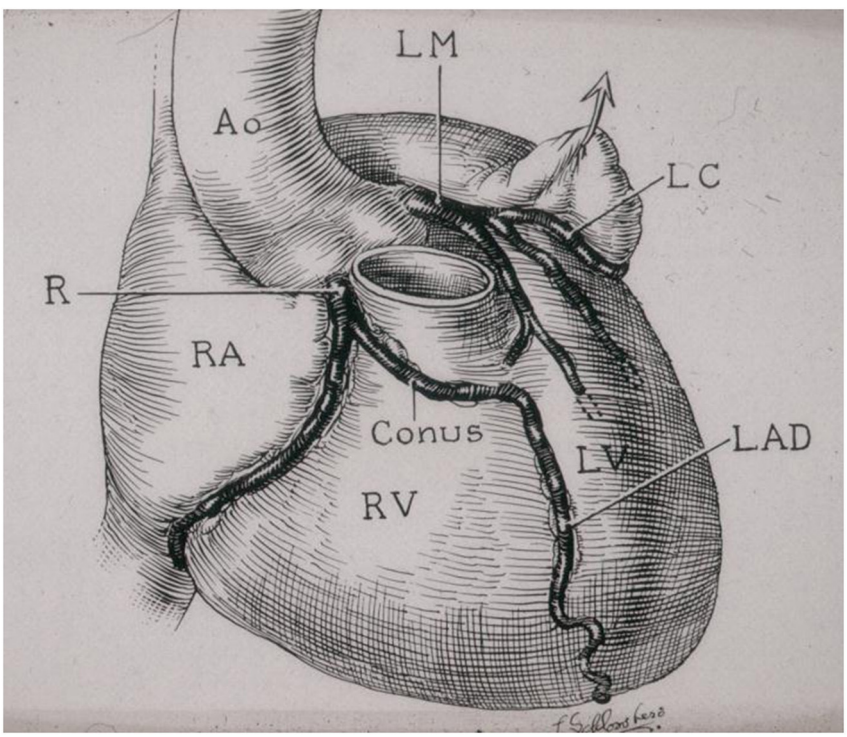

FIGURE 11 | Origin of the left anterior descending coronary artery from the right coronary artery. Note the anomalous proximal course in front of the pulmonary infundibular. From Roberts (6).

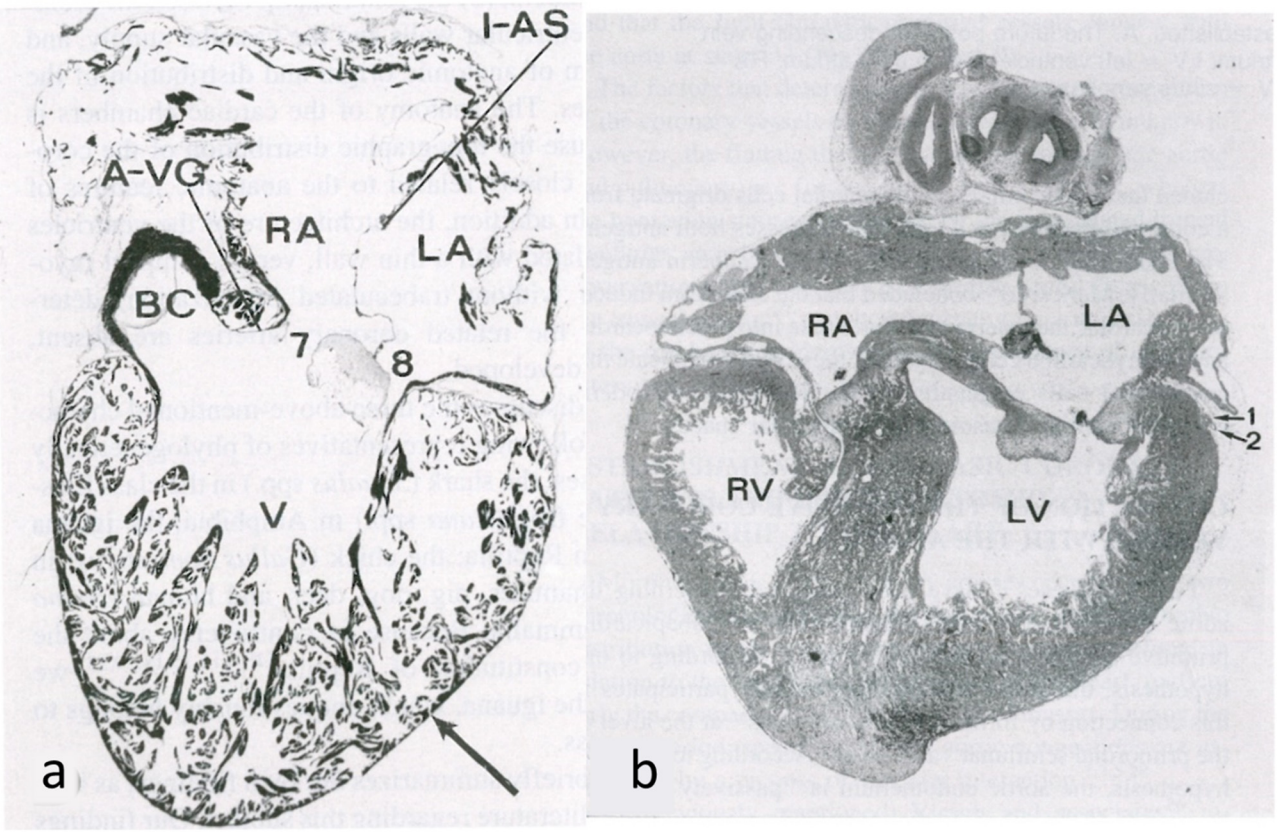

FIGURE 12 | Embryology of the myocardium. **(a)** Spongy myocardium from a mature fog with blood supply deriving directly from the endocardium of the ventricular cavities. **(b)** The myocardium of a fetal chick heart becomes compact, with blood supply deriving from the subepicardial vasculature. From de la Cruz et al. (13).

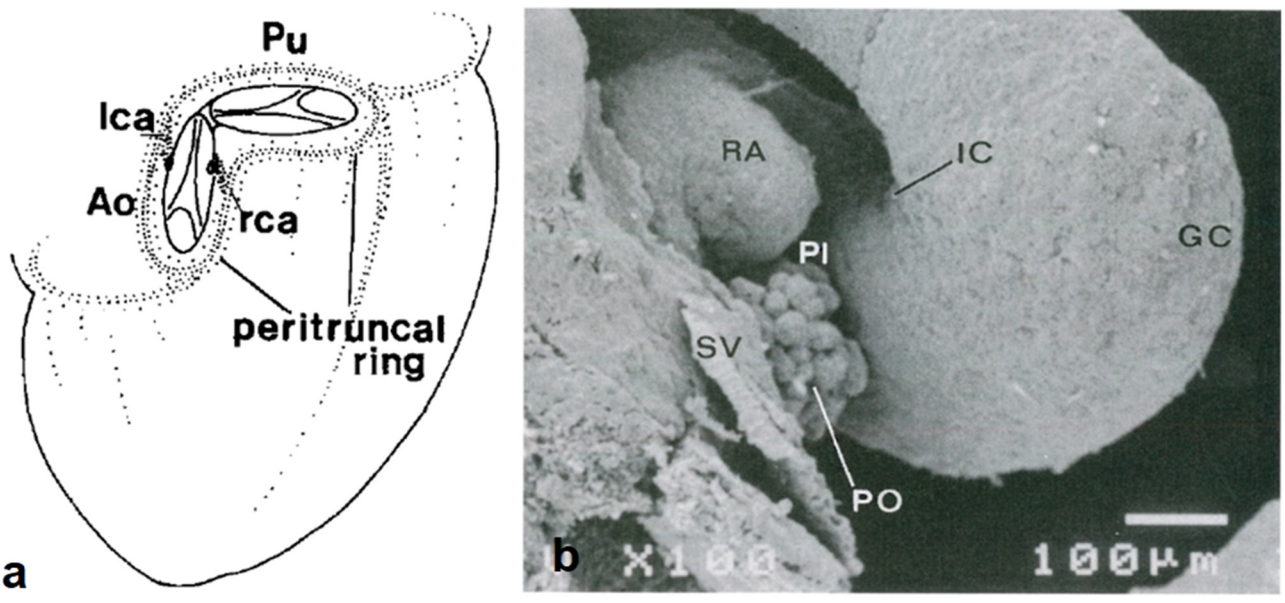

FIGURE 13 | Origin of coronary arterial stems from the peritruncal epicardial ring. **(a)** From Bogers et al. (17). **(b)** From de la Cruz et al. (13).

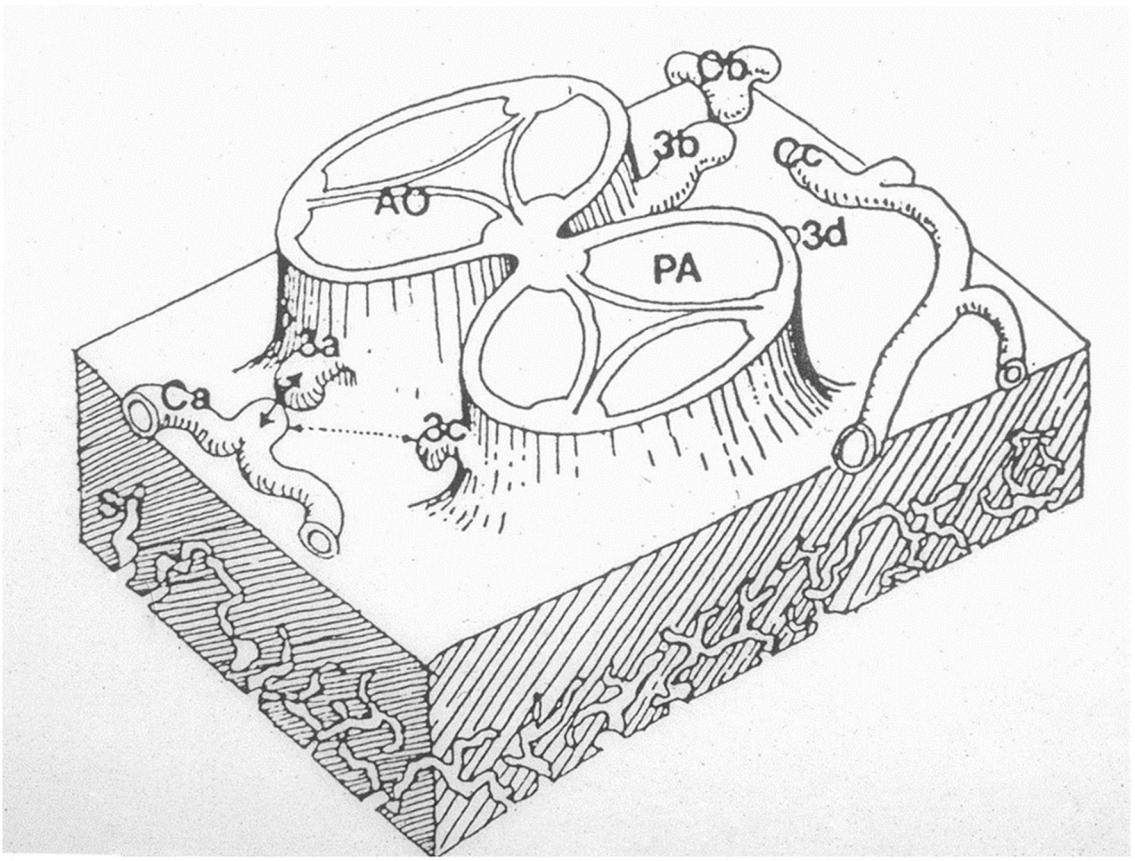

FIGURE 14 | The hypothesis according to which sprouts or buds arise from the facing aortic sinuses and make contact with the subepicardial coronary vasculature. From Angelini (18).

the connection, arteries with the aorta, and veins with the sinus venosus.

A subepicardial network of cells ("bioepicardial organ") surrounds the orifices of the great arteries (peritruncal ring) (**Figure 13**) and eventually connects with the facing aortic sinuses.

The question is whether the development of CA origin is a matter of ingrowth or outgrowth. There are two hypotheses to explain the connection.

The first is the outgrowth hypothesis, namely, the development of sprouts or buds from the aortic wall of facing sinuses, capturing the peritruncal ring of coronary subepicardial arterial vasculature (13, 18) (**Figure 14**).

The second developmental hypothesis, proven by serial sectioning of both human and rat embryos, is supported by the observation that the prongs of the peritruncal ring penetrate the aortic wall and make contact with the endothelial lining of the aorta (17, 19).

Recent investigations (20) confirmed that the proximal CAs do not grow from the aorta; on the contrary, they grow into the aorta from the peritruncal ring of the subepicardial vascular plexus (**Figure 15**).

A consensus document from the Development, Anatomy, and Pathology Working Group of the European Society of Cardiology (21) was in favor of the ingrowth hypothesis with a statement that deserves full quotation "…CAs were originally thought to form by angiogenesis from the aortic root endothelium" (22). "Angiogenesis implies the formations of new vessels from pre-existing ones, mostly by means of controlled endothelial sprouting" (23). "Indeed, until the late 1980s, it was thought that CAs entirely derived from an aortic endothelial outgrowth that would expand to form the complete coronary system, including coronary veins. Further research in avian models (19, 24–26) partially argued against, demonstrating that: (i) prospective CA endothelial cells do not bud from the aortic root, but instead grow into the aortic wall from an aortic peritruncal plexus to connect to the systemic circulation, most likely under the guidance of vascular endothelial growth factor (VEGF-C) and periaortic cardiomyocytes (27) and (ii) at least part of the early arterial coronary vascular system forms through a process of vasculogenesis…and subsequent fusion of endothelial cell clusters to form new blood vessels" (28).

As CA stems connect the aorta to the ventricular coronary tree, Thevenieu-Ruissy et al. did an investigation in both

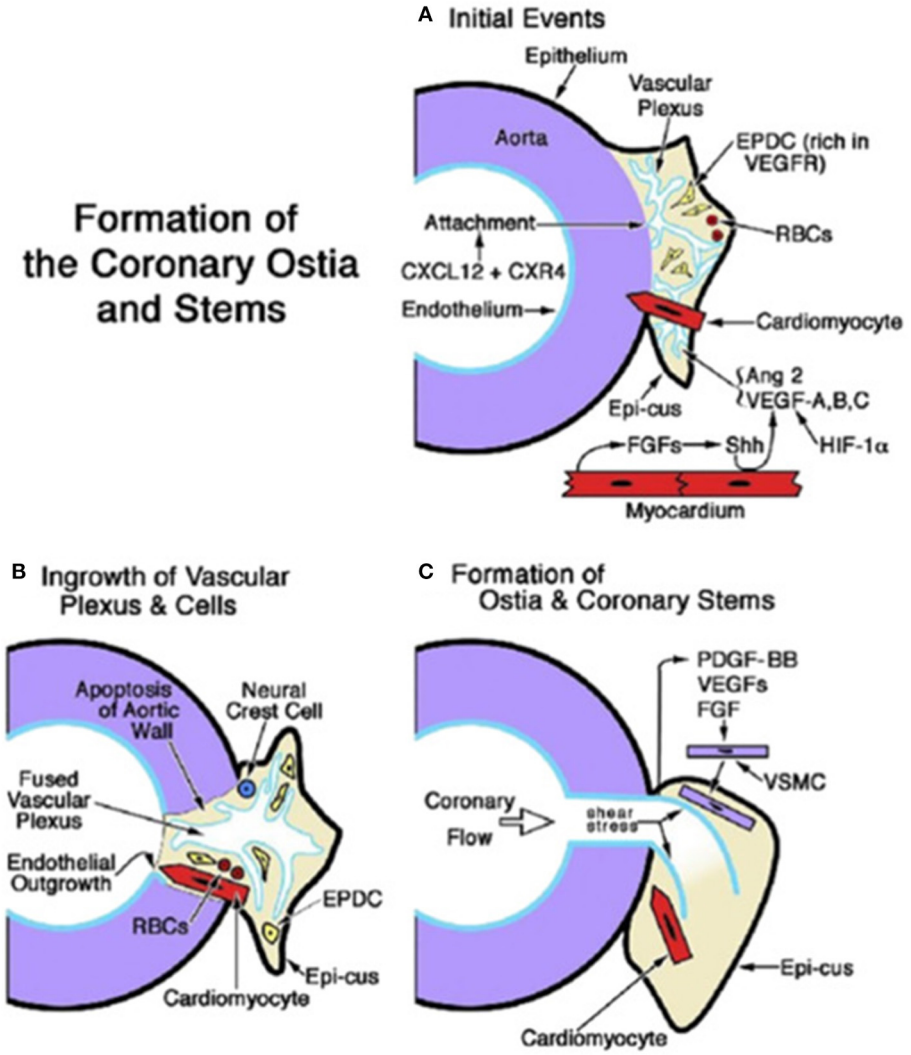

FIGURE 15 | Embryology of coronary artery orifices and main stems. **(A)** Formation of the coronary ostia and stems is initiated when the capillary ring that encircles the aortic root expands and attaches as a vascular plexus (in response to CXCL12 + CXR4). The sites of ostial formation are adjacent to an epicardial cusp (Epi-cus), a thickened portion of the subepicardium that contains epicardium-derived cells (EPDCs) that are rich in Vascular endothelial growth factor (VEGF) receptors and erythroblasts [red blood cells (RBCs)]. Cardiomyocytes guide the attachment of the vascular plexus. Fibroblast growth factors (FGFs) from the myocardium promote Sonic hedgehog (Shh) signaling, which, together with hypoxia inducible factor-1 (Hif-1), stimulates VEGFs and angiopoietin (Ang) 2, thus facilitating angiogenesis of the vascular plexus. **(B)** Myocardium-derived cardiomyocytes and neural crest cells facilitate the entry of the vascular plexus into an opening in the aortic wall, created by apoptosis. An endothelial ingrowth demarcates the pathway of the ostium formation. **(C)** The onset of coronary flow and shear stress is key to the remodeling of the vascular plexus. Differentiation, migration, and attachment of vascular smooth muscle cells (VSMCs) are influenced by (1) platelet-derived growth factor (PDGF)-BB activation in endothelial cells and the ligand's interaction with PDGFR-β in VSMC progenitors; and (2) the influence of VEGFs and fibroblast growth factors (FGFs). From Tomanek and Angelini (20).

wild-type and Tbx1 null mice embryos (29). They demonstrated that a periarterial plexus bridges limited outgrowth of the aortic endothelium with the ventricular plexus during CA stem development, supporting the hypothesis that outgrowth of aortic endothelium contributes little to proximal CA stems.

Septation of the arterial pole of the heart (42 days in the human embryo) precedes the appearance of coronary ostia when cells from the peritruncal ring migrate into the aortic root. Septation therefore cannot be responsible for the final position of coronary orifices.

Formation of the left CA precedes the right CA. Moreover, different from the tunica media of the ascending aorta, the tunica media of the CAs does not derive from the neural crest.

Cellular cross talks and signaling pathways (notch and hippo signals, transcription factors, angiogenic molecules, and apoptosis) take place (30–34). VEGF plays a crucial role in the development of coronary ostia and main stem formation (20) (**Figure 15**). Absence of VEGF was shown to inhibit ostia formation. Epicardial inhibition, reducing apoptotic remodeling at the ventricular–arterial junction, alters vascular connection

with the aorta and may produce CA anomalies equal to those observed in humans (35).

Why the primitive subepicardial coronary arterial vasculature tends to connect with the facing aortic sinuses, instead with facing pulmonary sinuses, is still unknown. The explanation cannot be the posterior position of the aorta since in transposition of the great arteries (TGA), where the aorta is anterior, the CA regularly connects with the facing sinuses of the aorta. An anomalous origin of a coronary artery from the posterior pulmonary artery in TGA is indeed extremely rare (36, 37).

AUTHOR CONTRIBUTIONS

GT designed and drafted the work. CF, MP, CB, and SR revised the work. All authors contributed to the article and approved the submitted version.

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Computed Tomography Derived Coronary Triangulated Orifice Area—Deduction of a New Parameter for Follow-up After Surgical Correction of Anomalous Aortic Origin of Coronary Arteries and Call for Validation

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Introduction: Anomalous aortic origin of a coronary artery (AAOCA) from the opposite sinus of Valsalva is a rare congenital abnormality. Computed tomography angiography (CTA) is primarily used as a diagnostic tool to evaluate the anatomy and identify potentially malignant AAOCA variants. Limited data is available on the role of CTA during postoperative follow-up. We aimed to develop an objective CTA derived parameter for diagnostic evaluation and follow-up after surgical correction of AAOCA and correlate the anatomical features to the postoperative outcome.

Methods: All consecutive patients who underwent surgical repair of AAOCA from 2001 to 2018 and had pre and postoperative CTA imaging available were included. A retrospective analysis of the pre- and postoperative CTA and the outcomes was performed. The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of operated coronary artery. To allow an accurate evaluation of the effective orifice area at diagnosis and after surgical repair we deduce and propose a new parameter—the coronary triangulated orifice area (CTOA).

Results: Out of the 54 patients who underwent surgical treatment for AAOCA, 11 fulfilled the inclusion criteria. The median follow-up was 19 months [IQR 3;42]. The mean age at surgery was 41 ± 16 years, with six patients (55%) being male. Postoperatively, the angle between the proximal coronary artery and the aortic wall increased from 20 ± 5° to 28 ± 9° ($p < 0.01$) and ostial diameter in the transversal plane increased from 4.1 ± 2.5 mm to 6.2 ± 2.7 mm ($p < 0.01$). The median CTOA increased significantly from 1.6 mm² [IQR 0.9;4.9] to 5.5 mm² [IQR 3;11.8] ($p < 0.005$). During follow-up, in three patients a restenosis of the operated coronary artery was suspected. In these patients, the CTOA only showed a limited postoperative increase of ≤ 1.4 mm².

Conclusions: CTA can play an important role in the evaluation of the pre- and postoperative anatomy in AAOCA patients. CTOA may be of use in conjunction with the acute angle take-off and ostial diameter order to comprehensively evaluate the operated ostium after unroofing or patch angioplasty.

Keywords: computed tomography angiography, surgical correction, coronary triangulated orifice area, clinical outcome, coronary anomaly, anomalous aortic origin of a coronary artery

INTRODUCTION

Anomalous aortic origin of coronary arteries (AAOCA) from the opposite sinus of Valsalva is a rare congenital abnormality affecting 0.03–0.1% of the population and involving an abnormal origin and course of a coronary artery (1, 2). Depending on anatomical and clinical characteristics, some AAOCA variants are associated with an increased risk of ischemia and sudden cardiac death in children and active young adults and are designated malignant (3, 4). Surgical repair of malignant AAOCA is reported to be safe and effective (4–6). However, data on long term follow-up is currently lacking and there are remaining concerns on identifying the patients at risk of suboptimal surgical outcomes and long-term complications.

In adults, coronary anatomy can be accurately evaluated using computed tomography angiography (CTA) (7, 8) and CTA is the imaging modality of choice to assess the AAOCA origin and course, degree of luminal narrowing, its relationship to surrounding structures and concomitant obstructive coronary artery disease (9). The various pathologic aspects of malignant AAOCA all contribute to a significantly reduced functional ostial area of the anomalous coronary artery causing ischemia and potentially lethal arrhythmias. Limited data is available on the role of CTA during follow-up and the expert consensus on AAOCA does not reflect on the role of CTA in the postoperative setting (10). A number of studies refer to the status of the neo-ostium after surgery (11–15). However, to our knowledge, no objective non-invasive method for measuring and quantifying the functional ostium has been established, and the spectrum of application of CTA in the postoperative setting is yet to be fully explored (11–14). Given the prominent role of surgery in the adequate management of this often young patient group in need of life long surveillance, it is of interest to know how the (neo-) ostial parameters are effected by the surgical interventions and to correlate this with the clinical outcomes (6).

In this study we compared the pre- and postoperative CTA features of a series of patients who underwent surgical correction of malignant AAOCA and deduce a new CTA derived parameter, the coronary triangulated orifice area (CTOA). The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of operated coronary artery during follow-up.

MATERIALS AND METHODS

All consecutive patients ($n = 54$) who underwent surgical repair of AAOCA from the opposite sinus of Valsalva at the Leiden University Medical Center between 2001 to 2018 were reviewed. In that era, postoperative CTA was not a part of routine clinical follow-up and was performed at discretion of the cardiologist. Adolescent and adult patients who had adequate pre- and postoperative CTA imaging available were approached for informed consent and included in further analysis. Patients unable or unwilling to communicate with the research team were excluded. Cases where CTA imaging was of insufficient quality were excluded. Patient data were collected from the electronic medical file system (EPD-Vision®, Leiden) and included: gender, age, comorbidities (a.o. diabetes, hypertension, previous ischemic coronary artery disease), type of AAOCA (originating from left or right sinus of Valsalva), dominancy of the coronary system, presence of symptoms at diagnosis and at follow-up, diagnostic imaging techniques [CTA, coronary angiography or magnetic resonance imaging (MRI)], the surgical technique used (unroofing or ostioplasty),

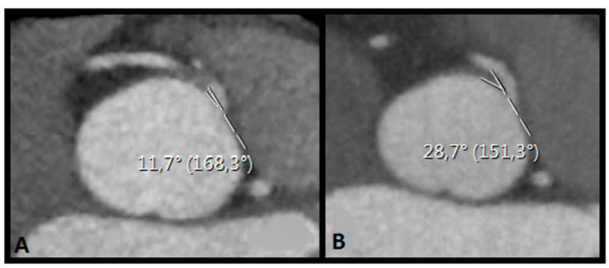

FIGURE 1 | Take-off angles preoperatively **(A)** and postoperatively **(B)** obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium, in the same patient. The angle increased from 11.7 to 28.7°.

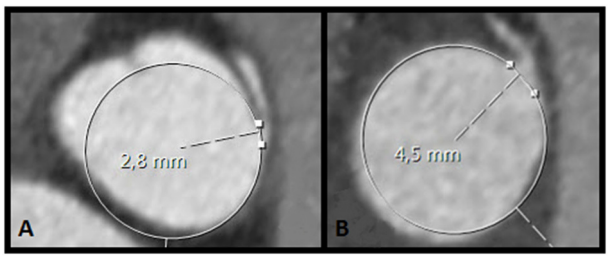

FIGURE 2 | Ostial diameter in the transverse plane preoperatively **(A)** and postoperatively **(B)** obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium, in the same patient. The ostial diameter increased from 2.8 mm to 4.5 mm.

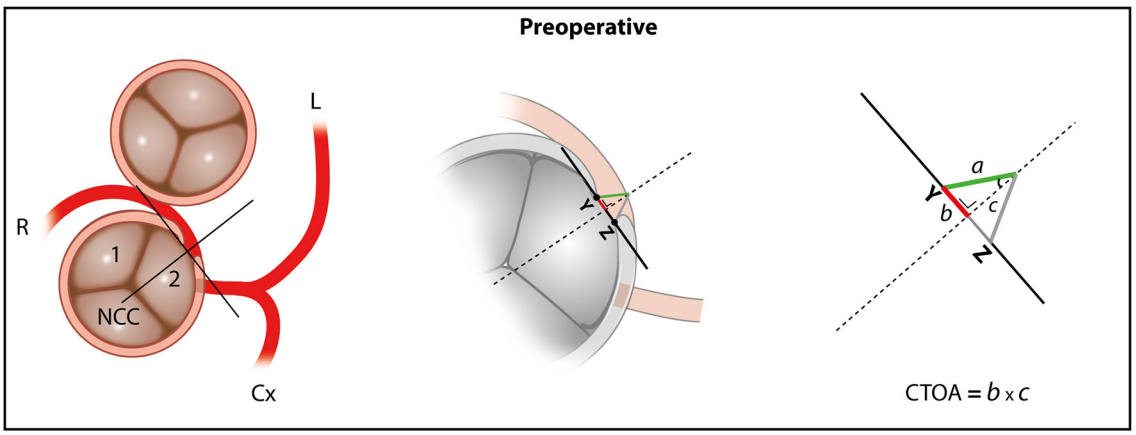

FIGURE 3 | Schematic representation of the coronary triangulated orifice area (CTOA). CTOA = 2 × (½ × b × c) = b × c; b = ½ ostial diameter; c = the depth of the triangle measured on CTA. The effective coronary ostial area as measured by the CTOA increases after the surgical correction of the coronary anomaly. R, right coronary artery; L, left coronary artery; Cx, circumflex coronary artery; NCC, non-coronary cusp; The area of the triangle is formed by 2 equilateral triangles. Y, representing the acute angle the outer edge of the orifice point; Z, representing the end of the ostium of the coronary anomaly; b, the base of the triangle; c, the depth of the triangle.

concomitant procedures, adverse cardiac events at follow-up (re-operation or percutaneous coronary intervention (PCI) on the operated coronary artery). The study focused on medium-term outcomes. Therefore, in hospital events in the postoperative setting (<1 month) were excluded.

Patients were scanned using a 64-row CT scanner (Aquillion64, Toshiba Medical Systems, Otawara, Japan; General Electrics LightSpeed VCT, Milwaukee, WI, USA) or with a 320-row CT scanner (Aquilion ONE, Toshiba Medical Systems) using an ECG-triggered protocol. Before scanning patients' heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding 65 b.p.m. received 50–100 mg oral metoprolol, or 5–10 mg metoprolol intravenously. For optimal heart phase selection, retrospective ECG gating was used. CTA images were reviewed with PACS® software and were reconstructed in multiphase data sets. Datasets were reconstructed from the retrospectively gated raw data with an effective slice thickness of 0.5–0.625 mm using standardized window/ level software CTA settings for vascular structures. Coronary artery anatomy was evaluated using the reconstruction dataset with the least motion artifacts, ranging from the end-systolic phase and mid-to end diastolic phase, depending on the heart rate of the patient.

All scans were evaluated by the primary investigator (FMMM), sub-investigator (DBHV) and an experienced radiologist (HJL). Multiplanar reconstructions in the oblique view at the level of the AAOCA ostium using the smallest available slice thickness were obtained and assessed for (1) the presence of an acute angle take-off (**Figure 1**), defined as the angle between the proximal coronary artery and the tangent line to the aortic wall and (2) the ostial diameter of the AAOCA (**Figure 2**) (16, 17).

Since the ostial diameter is a linear parameter and does not take into account the intraluminal depth of the (operated) coronary ostium, it might not fully reflect the functional ostial area of the coronary artery or the benefit attained after surgical correction. This can, in particularly, be the case in patients after surgical patch angioplasty. We therefore deduced the concept of a coronary triangulated ostial area (CTOA) and the methodology of its quantification, which although a 2-dimensional technique, does take into consideration the ostial depth (**Figure 3**).

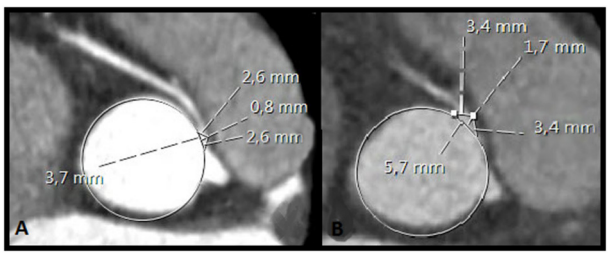

FIGURE 4 | Coronary triangulated orifice area (CTOA) pre- and postoperatively in the same patient (**A,B**, respectively). The ostial diameter increased from 3.7 to 5.7 mm. The CTOA increased from 1.5 to 4.9 mm².

A step by step guide on how to obtain the necessary reconstructions and measure the CTOA can be found in the online supplement (**Supplementary Material**). In short, a double oblique multiplanar reformation (MPR) reconstruction perpendicular to the aortic valve annulus and parallel to the ascending aorta should be obtained. Next, the investigator scrolls through the double oblique MPR of the aortic root until the center of the orifice of the AAOCA is encountered. A circle is then projected in the orifice of the AAOCA to define where the vessel wall of the AAOCA takes off from the aorta. Next, a tangent line is drawn from the inner edge of the orifice point "Y" to the opposing end of the ostium "Z." A perpendicular line is placed in the middle of the tangent line which extends to the end of the proximal part of the vessel. Two equilateral triangles are then

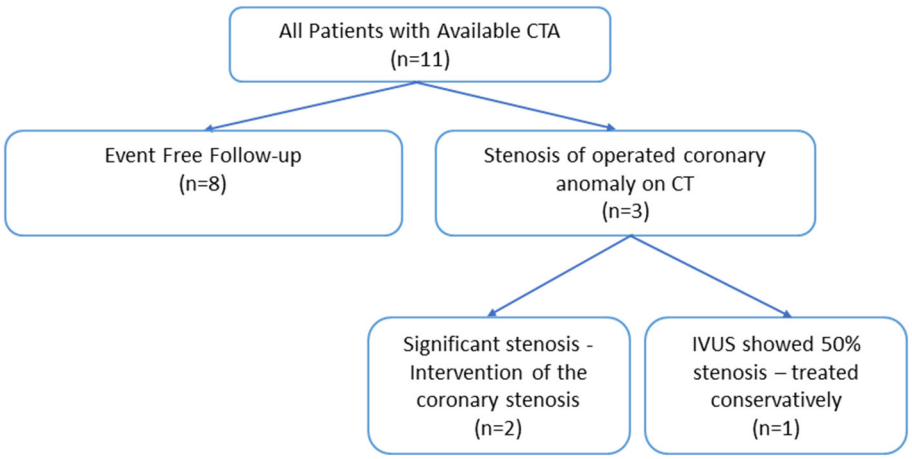

FIGURE 5 | Schematic overview of the study cohort and the outcomes. CTA, computed tomography angiography; IVUS, intravascular ultrasound.

formed. The area of these two triangles combined is the CTOA. The formula that is used to calculate the area of the ostial triangle is: 2 × (½ x b x c), simplified as b x c. In this formula "b" is the length of the base of the triangle (equal to ½ of the ostial diameter obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium) and "c" the depth of the triangle measured on CTA (**Figures 3**, **4**). To assess the interobserver agreement of CTOA, measurements were repeated by DBHV, blinded to the measurements of FMMM.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics package V.23 (Armonk, New York, USA). Normally distributed continuous data are displayed as mean ± standard deviation (SD) and non-normally distributed continuous data are displayed as median ± interquartile range [IQR1; IQR3]. Proportions are displayed as numbers (percentages, %). For the comparison of values pre- and postoperatively, paired samples *t*-tests or Wilcoxon rank-sum tests were used as appropriate. Interobserver agreement was visually assessed by calculation of the mean difference between observed values and constructing the limits of agreement (±1.96 SD of the difference, thus including 95% of measurements) according to Bland and Altman (18). In addition interobserver agreement was statistically assessed with calculation of intraclass correlation coefficients (ICC). All reported *p*-values were two-sided, and a value of $p < 0.050$ was considered statistically significant.

RESULTS

Of the 54 consecutive patients, 11 were included for further analysis (**Figure 5**). Patient characteristics are shown in **Table 1**. The mean age at surgery was 41 ± 16 years, with six patients (55%) being male. Preoperatively, one patient had an anomalous left coronary artery LCA (patient 5), all other patients had an anomalous RCA. All patients had an interarterial course with the vessel take-off at or above the pulmonic valve commissure, with the artery traversing between the aorta and the right ventricular outflow tract. Nine patients (82%) had a right coronary dominant system. The majority of the patients underwent coronary artery unroofing (82%). Two patients (18%, patient 5 and 11) underwent an enlargement of the ostium with a saphenous vein patch.

The median interval from operation to CTA was 6 months [IQR1;27]. **Figure 5** shows a schematic representation of the CTA findings and consequences and **Table 2** shows the patient details. The interobserver variability of the CTOA was evaluated. The intraclass correlation coefficient (ICC) for CTOA is good (ICC = 0.947, $p < 0.050$ for the preoperative measurements and ICC 0.874, $p < 0.050$ for the postoperative measurements). The measurements of both observers are visualized in Bland–Altman plots (**Figure 6**). This visually confirms that the limits of agreement (dotted lines) of CTOA are acceptable.

A restenosis of the operated coronary artery was suspected in 3/11 patients (27%) based on the CTA (patient 3, 7, and 11). This was further evaluated with coronary artery angiography (CAG) and intravascular ultrasound (IVUS) in all cases. Patient 3 experienced non-anginal complaints and CTA performed 43 months postoperatively suggested an ostial stenosis of the RCA. During CAG a 50% ostial lesion of the RCA was visualized and considered hemodynamically non-significant. The patient was treated conservatively and symptoms resolved. Patient 7 had typical anginal complaints and underwent a CTA that suggested a significant ostial stenosis of the RCA. This was confirmed at CAG with concomitant IVUS evaluation (persistent ostial narrowing after unroofing, visual stenosis of up to 80%, minimum lumen area of proximal RCA 3.3 mm^2) and the patient underwent a PCI with stent implantation. Patient 11 also underwent a CTA 2 months after surgery due to non-anginal complaints that revealed an ostial lesion of the RCA. A CAG with IVUS assessment was performed and this revealed an ostial stenosis of (60–70%) and a 70% stenosis distally of the venous patch with minimum lumen area of 3.3 and 3.5 mm^2, respectively. This was treated with PCI with implantation of 2 stents (with overlap).

TABLE 1 | Baseline characteristics of the patient cohort described in this study.

Patient characteristics	All patients ($n = 11$)
Male, *n* (%)	6 (55)
Age at surgery, years, mean (SD)	41 (16)
Diabetes mellitus *n* (%)	1 (9)
Hypertension *n* (%)	2 (18)
Previous ischemic coronary artery disease *n* (%)	0
Hypercholesterolemia *n* (%)	3 (27)
AAOLCA *n* (%)	1 (9)
AAORCA *n* (%)	10 (91)
Right dominant system *n* (%)	9 (82)
Symptoms present, *n* (%)	10 (91)
Primary presentation, *n* (%)	
Suspicion of ischemia	8 (73)
Aborted sudden cardiac death	2 (18)
Incidental finding	1 (9)
Diagnostic imaging techniques, *n* (%)	
CTA	11 (100)
CAG	8 (73)
MRI	2 (18)
Interval to follow-up CTA, median months [IQR1; IQR3]	6 (1, 27)
Indication for follow-up CTA, *n* (%)	
Follow-up	4 (36)
Symptoms	
Non-anginal complaints	6 (43)
Typical complaints	1 (9)
Surgical technique, *n* (%)	
Unroofing	9 (82)
Ostioplasty	2 (18)
Concomitant procedure, *n* (%)	
Pulmonary artery patch augmentation	1 (9)

AAOLCA, anomalous aortic origin of the left coronary artery; AAORCA, anomalous aortic origin of the right coronary artery; CAG, coronary angiography; CTA, computed tomographic angiography; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation.

A retrospective analysis of the pre- and postoperative CTA characteristics was performed, **Table 3**. The angle between the proximal coronary artery and the aortic wall significantly increased from $20 \pm 5^{\circ}$ to $28 \pm 9^{\circ}$ ($p < 0.01$) postoperatively. The ostial diameter, significantly increased from 4.1 ± 2.5 mm to 6.2 ± 2.7 mm postoperatively ($p < 0.01$).

The median CTOA increased significantly from 1.6 mm² [IQR 0.9;4.9] to 5.5 mm² [IQR 3;11.8] ($p < 0.005$). In every patient there was a consistent increase in CTOA compared to preoperative imaging (**Table 3**). Interestingly, the 3 patients suspected of a restenosis, based on the follow-up CTA all had an only marginal CTOA increase of $\leq$ 1.4 mm² (**Supplementary Table 1**).

DISCUSSION

Computed tomography angiography (CTA) is an important tool for evaluation of the pre- and postoperative anatomy in AAOCA patients. Previously described high-risk findings in coronary artery anomalies include an acute angle take-off of the coronary artery relative to the aorta, an initial aortic intramural course, a "slit like" coronary artery ostium and coursing of the artery between the aorta and the pulmonary trunk. In this study, we compare several objective CTA parameters before and after surgical correction of AAOCA. To allow an accurate evaluation of the effective orifice area we deduce a new parameter—the coronary triangulated orifice area (CTOA). We evaluate the CTOA and correlate the anatomical features to the postoperative outcome in our patient cohort. The main findings of this study are that after surgical correction, the angle between the proximal coronary artery and the aortic wall and the ostial diameter both increase significantly. The CTOA also shows a significant increase postoperatively. Of interest, in patients with a restenosis of the operated coronary artery, the CTOA only showed a very limited postoperative increase.

CTA is currently one of the preferred techniques to evaluate AAOCA. Guidelines provide a Class I recommendation for either CT or magnetic resonance imaging coronary angiography to be used as the initial evaluation method for coronary anomalies as these techniques have the ability to characterize multiple anatomical features of AAOCA (19). The AHA/ACC 2018 or the ESC 2020 guidelines, however, do not give guidance on how to use CTA in the postoperative setting of AAOCA (20). In the literature an acute angle is defined as the angle between the proximal coronary artery and the aortic wall of $<45^{\circ}$ (21, 22). It is measured as the angle between the plane formed by the ostium center to a point 5 mm along the vessel centerline, and a plane tangent to the aorta in multiplanar axial reconstruction at the level of the AAOCA ostium using the smallest available slice thickness (allowing for highest spatial resolution) (21, 23). In two autopsy studies an acute angle was frequently encountered in patients with AAOCA who presented with sudden cardiac death (24, 25). In our patient cohort we observed a significant increases in the angle postoperatively from $20 \pm 5^{\circ}$ to $28 \pm 9^{\circ}$ ($p < 0.01$). According to the current definition, however, the acute angle persisted in all of our patients. This suggests that the finding of an acute angle alone is not reflective of surgical success in a substantial number of patients and cannot as such be predictive of the clinical outcome.

Another parameter used to assess surgical success is shortening of the intramural segment of the AAOCA. Prior research illustrates that there is a high correlation in the use of CTA to identify an intramural course and direct anatomical findings during surgery, and that there is an association with the length of the intramural segment and prognosis of the patients (15, 22, 26). Histologically, an intramural coronary is defined as an coronary artery partly sharing the media of the aortic wall with no adventitia interposed (10, 27). However, this parameter is very hard to accurately delineate on CTA due to the spatial resolution of this technique. For this reason we did not measure the intramural segment in our study. Instead, we opted for measuring the ostial diameter on CTA and calculating the CTOA. This is a geometric derivative of the ostial diameter and ostial luminal depth. In our patient group surgery led to consistent improvement of CTOA from

TABLE 2 | Individual patient characteristics at surgery and follow-up.

Patient	Age at surgery (years)	AAOCA	Surgical technique	Interval to follow-up CTA (months)	Indication for follow-up CTA
1	20–25	RCA	Unroofing	6	Unknown
2	30–35	RCA	Unroofing	<1	Postoperative evaluation
3	56–60	RCA	Unroofing	43	Non-anginal complaints
4	45–50	RCA	Unroofing	2	Non-anginal complaints
5	10–15	LCA	Ostioplasty	<1	Postoperative evaluation
6	25–30	RCA	Unroofing	42	Non-anginal complaints
7	60–65	RCA	Unroofing	13	Typical complaints
8	45–50	RCA	Unroofing	27	Non-anginal complaints
9	55–60	RCA	Unroofing	25	Non-anginal complaints
10	45–50	RCA	Unroofing	1	Non-anginal complaints
11	25–30	RCA	Ostioplasty	2	Non-anginal complaints

AAOCA, anomalous aortic origin of coronary artery; CTA, computed tomography angiography; LCA, left coronary artery; RCA, right coronary artery.

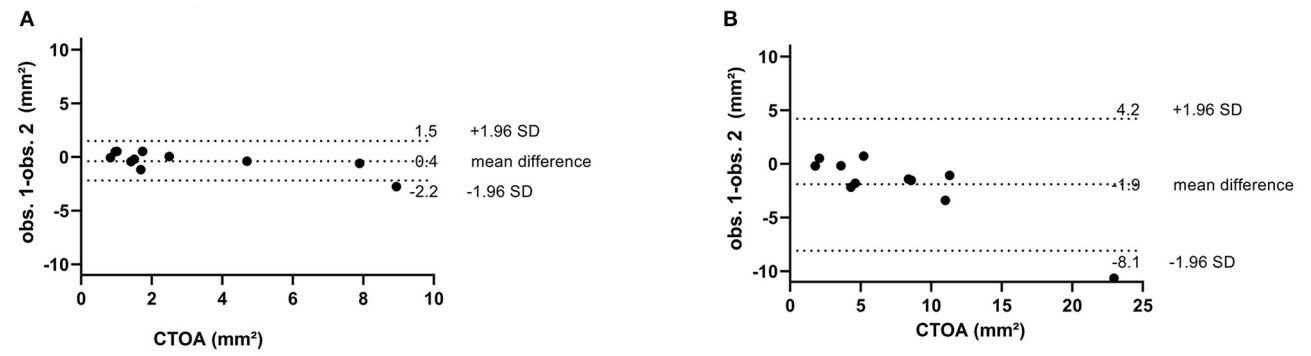

FIGURE 6 | Bland-Altman plots in **(A)** the preoperatively and **(B)** postoperative setting. The mean value of the CTOA is plotted on the x-axis and the difference between the two observers on the y-axis. The mean differences of all observations are close to zero, indicating no important bias between the two observers.

1.6 mm² [IQR 0.9;4.9] to 5.5 mm² [IQR 3;11.8] ($p < 0.005$), respectively. This parameter may be used to objectify the functional increase in the orifice surface area after surgery. This is particularly applicable in patch augmentation techniques and unroofing in which the ostium is widened. In our study 2 patients underwent PCI of the ostial segment of the operated coronary artery during follow-up. Although the mechanism is not entirely elucidated, ostial restenosis may be caused by fibrous scar tissue formation postoperatively (28). Of interest, in the patients who required PCI during follow-up, the CTOA only showed a very limited postoperative increase of < 1.4 mm² to an absolute CTOA of < 4mm² (**Supplementary Table 1**). It would be important to evaluate whether there is an absolute minimal ostial area required for preservation of coronary patency in the postoperative setting and whether a (limited) increase in CTOA has any prognostic value.

The majority of patients with high risk features of an AAOCA undergo unroofing, this was also the case with 9 out of 11 patients in the current series. With unroofing the (inside) aortic wall part of the intramural course is removed, creating an expanded ostium. The aim of this treatment is to discard the slit like orifice, acute angle, as well as the intramural course. An alternative method is enlargement of the ostium using a patch. This was performed in two patients in our study. Since the ostial diameter is a linear parameter and does not take into account the depth of the (operated) coronary ostium which is widened with unroofing and osteoplasty, it might not fully reflect the surgical benefit, the CTOA does take this depth into account. Our recent work showed that adolescents and adults with AAOCA can present with a wide range of complaints, only 35% of them being classified as "typical" according to the current criteria. Although surgical correction leads to a reduction of symptoms in the vast majority of patients, novel anginal complaints after surgery should prompt further evaluation for potential lesions of the operated coronary artery and suboptimal surgical outcomes (29). CTA can play an important role in the initial objective assessment of the postoperative ostium (and systematic comparison of the postoperative result to the preoperative anatomy). One should, however, realize that this is only measured during a fixed phase of the heart cycle, not allowing for the thorough evaluation of the dynamic component of AAOCA. The full spectrum of application of CTA in the postoperative setting is yet to be explored and no objective non-invasive method for measuring and quantifying the ostial area has been established. The current study is one step further to determine the optimal way to non-invasively quantify the coronary orifice area after surgery and

TABLE 3 | Pre- and postoperative CTA characteristics.

CTA Parameters	Preoperative ($n = 11$)	Postoperative ($n = 11$)	*P*-value
Acute angle take-off (°) mean ± SD	20 ± 5	28 ± 9	<0.001
Ostial diameter (mm) mean ± SD	4.1 ± 2.5	6.2 ± 2.7	<0.001
Coronary triangulated orifice area (mm²) median [IQR1; IQR3]	1.6 [0.9;4.9]	5.5 [3.7;11.8]	<0.005
No significant stenosis ($n = 8$) [IQR1;IQR3]	2.0 [1.5–7.4]	9.2 [5.4;12.5]	<0.005
≥50% stenosis ($n = 3$) [IQR1;IQR2]	0.9 [0.75;0.85]	1.9 [1.81;1.88]	0.011

CTA, computed tomography angiography; IQR interquartile range; SD, standard deviation.

correlate this with clinical outcomes and should be technically and clinically validated in the setting of the larger prospective cohort (30).

LIMITATIONS AND FUTURE PERSPECTIVES

Despite the role of the Leiden University Medical Center as a national referral center for patients with AAOCA, the patient cohort size is small, reflecting the rarity of the condition and the lack of (historical) structural CTA follow-up. Due to the retrospective nature of this study it is subject to inherent bias, including selection bias based on the clinical and anatomical characteristics of patients that were referred for surgery and therefore underwent more extensive preoperative testing and those with postoperative symptoms requiring further analysis and follow-up.

It is important to note that measurement of the CTOA requires strict adherence to a predefined protocol to ensure its reproducibility (particularly when looking to compare the pre- and postoperative anatomy), which may challenge its robust clinical implementation. Also, the accuracy of the CTOA may in practice be limited by the spatial resolution of the CTA. In theory, the highest in-plane spatial resolution achievable approaches 0.4 mm. In practice, coronary artery motion produces both spatial and temporal blurring, resulting in an effective spatial resolution closer to 0.5 mm (31). The current results, however, do provide us with potentially useful conceptual tools to evaluate surgical outcomes in patients with AAOCA and call for further prospective validation in a larger patient group. The potential of artificial intelligence in automated measurements of CTOA remains to be explored.

One should be aware of the inherent limitations of CTA, predominantly useful when evaluating "high risk" anatomical features, but lacking the ability to adequately asses the physiological consequences of an AAOCA. In the setting of AAOCA associated ischemia, future research should also take into account the functional (dynamic) consequences of these anatomical features and correlate CTA findings with functional evaluation at rest and during (physical) stress using a.o. intravascular ultrasound and fractional flow reserve assessment (32). Adrenalin and dobutamine infusions can be used to mimic physical exercise stress (increasing heart rate and stroke volume) according to the previously published protocols (32, 33). Multicenter studies with standardized preoperative and follow-up protocols are essential in this. To this aid a national protocol for evaluation and management of AAOCA patients has recently been initiated as part of the MuSCAT study (30).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article can be made available by the authors, without undue reservation.

ETHICS STATEMENT

All tests and procedures performed involving human participants were in accordance with the ethical standards of the institutional and national guidelines and with the 2013 Helsinki declaration or comparable ethical standards. Appropriate local scientific board approval was obtained for this retrospective medical record study. All patients provided consent for coded registration, analysis and publication of their data.

AUTHOR'S NOTE

Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

AUTHOR CONTRIBUTIONS

FM, PK, DV, HV, MJ, MH, HL, and AE conceived and designed the analysis, collected the data, contributed data or analysis tool, performed the analysis, and wrote the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.668503/full#supplementary-material

Step by Step Guide to measure CTOA.

1. Start in the standard axial plane at the level of the aortic valve annulus (**supplementary Figure 1**).
2. Perform a double oblique multiplanar reformation (MPR) perpendicular to the aortic valve annulus and parallel to the ascending aorta (**supplementary Figure 2**).
3. Scroll through the MPR (double oblique, short axis) of the aortic root until the center of the orifice of the AAOCA appears in the plane you are viewing (**supplementary Figure 3**).
4. Project a circle in the orifice of the AAOCA to define where the vessel wall of the AAOCA takes off from the aorta (**supplementary Figure 4**).
5. To measure the CTOA, draw a tangent line from the inner edge of the orifice point "Y" to the opposing end of the ostium "Z" (**supplementary Figure 5**).
6. A perpendicular line is placed in the middle of the tangent line which extends to the end of the proximal part of the vessel. Two equilateral triangles are then formed.
7. The area of these two triangles combined is the CTOA. The formula that is used to calculate the area of the ostial triangle is: $2 \times (½ \times b \times c)$, simplified as $b \times c$, where "b" is the length of the base of the triangle and "c" the depth of the triangle.

Supplementary Figure 1 | Step 1.

Supplementary Figure 2 | Step 2.

Supplementary Figure 3 | Step 3.

Supplementary Figure 4 | Step 4.

Supplementary Figure 5 | Step 5–7.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Congenital Coronary Artery Ring With Single Left Coronary Ostium and Fistula: A Previously Unreported Anatomy

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Background: Single coronary ostium concomitant with coronary artery fistula is a very rare congenital anomaly. Apart from that, the combination of a closed loop of the coronary artery has never been reported.

Case presentation: Herein, we present a 7-year-old girl diagnosed as single left coronary ostium with a giant coronary trunk, coronary artery to right ventricle fistula, and coronary artery ring. The coronary fistula was surgically ligated with off-pump strategy and the patient discharged on postoperative day 5 and free of symptoms during the 3 years of follow-up.

Conclusion: To our knowledge, the presented congenital coronary anomaly is the first to be reported in the literature with the name of congenital coronary artery ring with single left coronary ostium and fistula.

Keywords: coronary artery anomalies, single coronary ostium, giant coronary trunk, coronary artery fistula, coronary artery ring

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BACKGROUND

Single coronary artery (SCA) in which one coronary artery emerges from a single coronary ostium in the aorta, is a very rare angiographic feature in congenital coronary artery abnormalities (0.024 to 0.066%), with different subtypes depending on the course of the abnormal artery (1). SCA can be either an isolated congenital cardiac disease or be associated with other congenital abnormalities. SCA combined with coronary artery fistula (CAF) is very rare and few cases have been reported (2–5). It's worth noting that SCA combined with CAF and coronary artery ring (left and right main coronary artery communicate with each other and form a closed loop) is extremely rare and easily misdiagnosed. Here we report a rare case of a SCA originates from the right aortic sinus, forming a giant coronary trunk, and associated with CAF with right ventricle (RV). Furthermore, the right main coronary artery was connected with the left conus branch via the collateral branch while the left circumflex was communicated with the right coronary artery thus forming a closed loop (CAR as we defined). The anomalies were successfully corrected with operation in our hospital. The case is first reported as we reviewed the literature.

CASE PRESENTATION

A 7-year old girl with exertive chest tightness was referred to our institution. Physical examination was notable for a grade 3/6 systolic and diastolic cardiac murmur over the third left intercostal space. There was no other notable clinical findings during physical examination or medical history and no family history of cardiovascular disease. Electrocardiogram, Chest X-ray and laboratory tests were unremarkable. Transthoracic echocardiography demonstrated a right coronary artery-right ventricular fistula. Computed tomography and three-dimensional coronary artery computed tomography angiography (**Supplementary Video 1**) showed the left and right main coronary artery, the left anterior descending artery and the circumflex artery were enlarged and tortuous. There is an interruption between right sinus of Valsalva and the right main coronary artery (**Figure 1A**, arrow), single left coronary ostium with a giant coronary trunk (**Figure 1B**, arrow). A branch from the proximal end of right coronary artreatery was inserted into the right ventricle through a 7-mm fistula (**Figure 1C**, arrow). The right main coronary artery was connected with the left conus branch via the collateral branch while the left circumflex was communicated with the right coronary artery thus forming a closed loop at the base of the heart (**Figure 1D**). Ascending aortic angiography was performed and further confirmed this malformation (**Figure 2**, **Supplementary Video 2**). There was no other notable medical or surgical history and no family history of cardiovascular disease. Because of extreme vessel tortuosity and inability to deliver a catheter far enough distally, the coronary fistula was then surgically ligated with off-pump strategy (**Figure 3**). The patient discharged on postoperative day 5 and free of symptoms during the 3 years of follow-up (**Figure 4**).

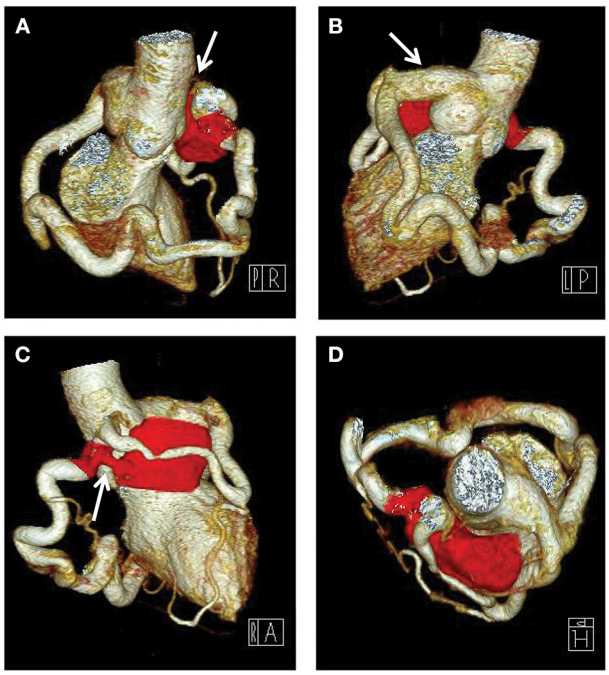

FIGURE 1 | Computed tomography angiography preoperatively showing that there is an interruption between right sinus of Valsalva and the enlarged and tortuous right main coronary artery (**A**, arrow), a single left coronary ostium with a giant coronary trunk (**B**, arrow), a 7-mm fistula into the right ventricle (Red) (**C**, arrow), the left and right coronary artery were connected with each other and formed a closed loop at the base of the heart **(D)**.

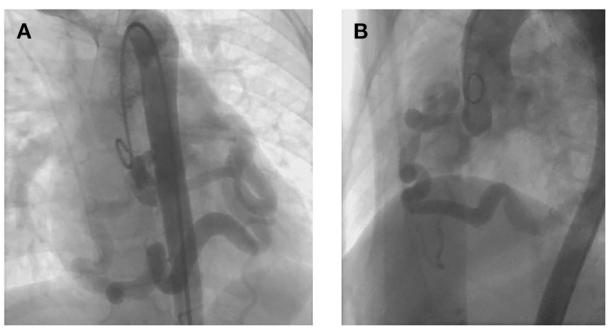

FIGURE 2 | Ascending aortic angiography preoperatively showing that the left and right coronary artery were enlarged and tortuous **(A)**, right coronary artery was detected secondly to the left one **(B)**, confirming the diagnosis of coronary artery ring with single left coronary ostium and fistula.

DISCUSSION AND CONCLUSIONS

Single coronary artery (SCA) is defined as an isolated coronary artery that arises from a single coronary ostium (with or without a coronary artery trunk) and provides blood supply to the entire myocardium (1). SCA could be classified into two main categories: left type (L) or right type (R) according to the origin location and anatomical distribution of branches. The categories were then designated as group I, II, or III according to the anatomical course. Group I had an anatomical course of either a RCA or LCA. Group II anomalies originate from the proximal part of the normal RCA or LCA, and cross the base of the heart before reaching the normal site of the inherent coronary artery. Group III specifically indicates the SCA arising from the right sinus of valsalva, with the left anterior descending (LAD) and left circumflex (LCx) branch originating separately from a common trunk (6). According to this classification, our patient presented with an L-II type of SCA originating from the left aortic sinus, and the right coronary artery was connected to the left conus branch via the lateral branch. It is important to know the origin and distribution of the whole coronary artery. In the presented case, the left circumflex was communicated with the right coronary artery thus a closed loop was formed at the base of the heart.

SCA can either be isolated or coexist with other congenital heart anomalies such as coronary arteriovenous fistula (3, 5), coronary aneurysm (7), patent foramen ovale (8),

Abbreviations: CAF, Coronary artery fistula; CAR, Coronary artery ring; LAD, Left anterior descending; LCx, Left circumflex; MDCT, Multi-detector computed tomography; RV, Right ventricle; SCA, Single coronary artery.

interventricular septal defect (9), patent ductus arteriosus (10), tetralogy of Fallot (11), transposition of great vessels (12), truncus arteriosus (13), and bicuspid aortic valve (14). CAF is a rare condition in which the coronary arteries communicate directly with the heart chambers or vessels. Selective angiography allows detection of SCA associated with CAF in most patients in the early stage (5). Preoperative multi-detector computed tomography (MDCT) coronary angiography, due to the non-invasive detection and the ability to reveal complex coronary artery anatomy, is recommended by the American Heart Association Committee to characterize these anomalies in conjunction with invasive coronary angiography (15, 16).

Most patients with CAF are asymptomatic at the early stage, but elderly patients may present with exertional chest pain, fatigue, palpitations, arrhythmias, congestive heart failure, or possibly sudden death (16, 17). CAF may result in preferential blood flow from coronary circulation to pulmonary circulation, leading to the coronary-steal-related chronic myocardial ischemia (17). Vieussens' arterial ring (VAR) is a rare anatomic variant and refers to the collateral pathway between the conus branches of the right and left coronary arterie that was first described by Raymond de Vieussens (18). Four subgroups of VAR were found and defined as a collateral pathway originating from the right anterior conus artery, a collateral pathway passing in front of the pulmonary artery, a collateral pathway connecting the right and a collateral pathway connecting the left coronary artery circulation: VAR accompanying with and without vascular pathology like aneurysm or fistula (Type 1B and 1A, respectively), with a short LAD branch (Type 2) and with a single coronary artery anomaly (Type 3) (19). In the presented case, the right main coronary artery was connected with the left conus branch via the collateral branch while the left circumflex was communicated with the right coronary artery thus forming a closed loop at the base of the heart (**Figure 1D**), which was unlike the subtypes of VAR and was a previously unreported anatomy. Thus, we named it the congenital coronary artery ring or Yang's ring. However, there are no treatment guidelines or follow-up recommendations currently. Management of these anomalies remains controversial, especially in asymptomatic patients. Various treatment modalities such as coil embolization, catheter-mediated stent occlusion, and surgical ligation are available (17). Catheter techniques are difficult or impossible in a small percentage of patients, due to extreme vessel tortuosity and inability to deliver a catheter far enough distally (20). Because of the high rate of late symptoms and complications, especially when the shunt is significant (Qp/Qs ratio > 1.5), early surgery is an optimal treatment in the case of SCA combined with CAF (5, 21). In the present case, the vessels are extreme tortuous and inable to deliver a catheter far enough through the coronary truck. Thus, a surgically ligated with off-pump strategy was recommended.

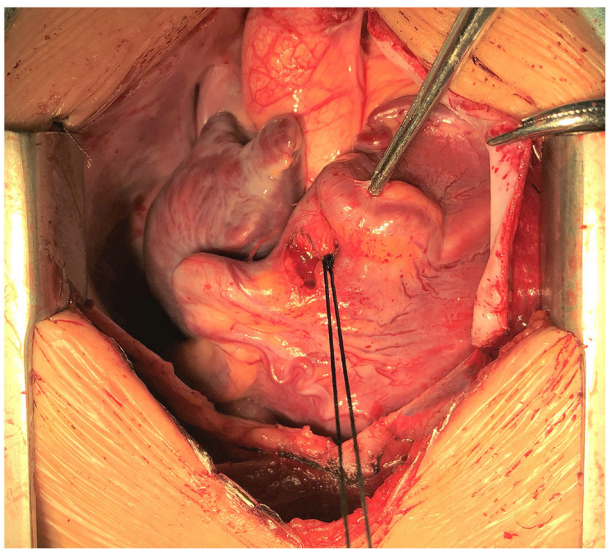

FIGURE 3 | Intraoperative view showing that the fistula was ligated with off-pump strategy.

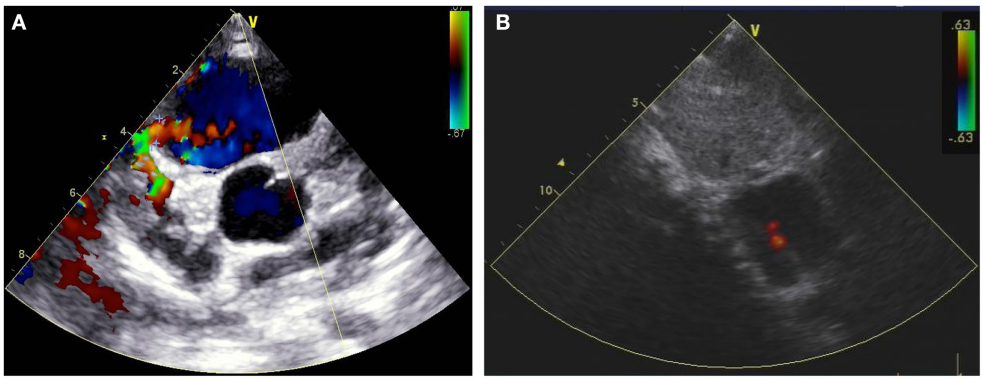

FIGURE 4 | Transthoracic echocardiography showing that a 6.28-mm coronary fistula into the right ventricle (**A**, arrow) was detected preoperatively, and undetectable 1 week post-surgical ligation **(B)**.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, Changsha, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ST and CF drafted the manuscript. CF and JY designed the study. CD, MT, and JY revised the manuscript. ST, MT, and JY were responsible for the collection of data or analysis. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.699529/full#supplementary-material

Supplementary Video 1 | Three-dimensional coronary artery computed tomography angiography: A giant coronary trunk from left coronary sinus then divide into two main branches. The left and right main coronary artery, the left anterior descending artery and the circumflex artery were enlarged and tortuous. A branch from the proximal end of right coronary artery was inserted into the right ventricle through a 7-mm fistula. The right main coronary artery was connected with the left conus branch via the collateral branch while the left circumflex was communicated with the right coronary artery thus forming a closed loop.

Supplementary Video 2 | Ascending aortic angiography: Confirming the diagnosis of single left coronary ostium with a giant coronary trunk, right coronary artery-right ventricular fistula and a coronary artery ring.

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Predictive Value of Gensini Score in the Long-Term Outcomes of Patients With Coronary Artery Disease Who Underwent PCI

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Objective: Gensini score is an effective tool used to evaluate the severity of coronary artery disease (CAD). Whether the Gensini score has predictive value for the clinical outcomes of patients with CAD after percutaneous coronary intervention (PCI) has not been investigated.

Methods: All patients were from the Clinical Outcomes and Risk Factors of Patients with Coronary Heart Disease after PCI (CORFCHD-PCI), a retrospective cohort study involving 5,672 patients with CAD who underwent PCI, such as 2,110 patients with diabetes and 3,562 patients without diabetes, from January 2008 to December 2017. Patients were divided into three groups according to the tertile of Gensini score: first tertile (Gensini score <11 points), second tertile (Gensini score 11–38 points), and third tertile (Gensini score >38 points). The median follow-up time was 31.0 (interquartile range, IQR: 30.0) months. Compared the differences in clinical outcomes between the groups. Multivariate Cox regression analyses were performed to assess the predictive value of the Gensini score for outcomes over up to 10 years of follow-up.

Results: In the population without diabetes, there were significant differences between the three groups in the incidences of all-cause mortality (ACM, $p = 0.048$), cardiac mortality (CM, $p = 0.024$), major adverse cardiovascular (CV) events (MACEs, $p = 0.006$), and major adverse cardiovascular and cerebrovascular events (MACCEs, $p = 0.009$). In the population with diabetes, there were significant differences between the three groups in the incidences of ACM, CM, MACEs, and MACCEs (all $p < 0.001$). After multivariate Cox regression analyses, in the population without diabetes, the respective risks of ACM, CM, MACEs, and MACCEs were increased 89.9% [hazard ratio (HR) = 1.899, 95% CI: 1.285–2.807, $p = 0.001$], 115.1% (HR = 2.151, 95% CI: 1.378–3.356, $p = 0.001$), 48.1% (HR = 1.481, 95% CI: 1.152–1.904, $p = 0.002$), and 49.8% (HR = 1.498, 95% CI: 1.176–1.907, $p = 0.001$) in the third tertile compared with those in the first tertile. In the population with diabetes, the respective risks of ACM, CM, MACEs, and MACCEs were increased 248.5% (HR = 3.485, 95% CI: 1.973–6.154, $p < 0.001$), 260.4% (HR = 3.604, 95% CI: 1.866–6.963, $p < 0.001$), 130.2% (HR = 2.302, 95% CI: 1.649–3.215, $p < 0.001$), and 119.8% (HR = 2.198, 95% CI: 1.600–3.018, $p < 0.001$) in the third tertile compared with those in the first tertile.

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Conclusion: The present study indicated that the Gensini score is an independent predictor of long-term adverse outcomes in patients with CAD who underwent PCI, and it has more predictive value in the population with diabetes.

Keywords: Gensini score, coronary artery disease, percutaneous coronary intervention, clinical outcomes, diabetic population

INTRODUCTION

Coronary artery disease (CAD) refers to heart disease caused by myocardial ischemia and hypoxia due to coronary artery stenosis or occlusion. It is the most common type of organ disease caused by atherosclerosis, and it is also the most common clinical cardiovascular (CV) disease (1). In recent years, with the innovation of surgical instruments and technical upgrading of percutaneous coronary intervention (PCI), more and more patients with CAD were treated with PCI, so as to obtain effective revascularization. However, in actual clinical work, it has been found that some patients have poor long-term outcomes after PCI treatment. Among patients who underwent PCI, patients with diabetes mellitus (DM) represent a high-risk subset compared with individuals without DM. Because DM is prone to have a greater atherosclerotic burden, diffuse, and long lesions in small-caliber vessels, and accelerated neointimal hyperplasia (2), patients with diabetes who underwent PCI have higher rates of adverse outcomes than patients without diabetes (3). Therefore, it is particularly important to choose a reasonable treatment strategy for CAD and identify the risk factors leading to poor outcomes. Morphology and degree of stenosis of coronary artery lesions determine the choice of the interventional treatment strategy. Currently, there are a variety of scoring systems used for quantitative analysis of coronary artery lesions and Gensini scoring is more commonly used in clinical practice. Gensini score fully considers the number, location, and degree of stenosis of coronary artery lesions, which is a more scientific evaluation standard of coronary artery lesions (4). At the same time, this scoring system has also been widely used in related studies on the clinical outcomes of CAD. At present, a number of studies have confirmed that the Gensini score can predict the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with different types of CAD (5, 6) and evaluate the severity of coronary artery lesions combined with certain biochemical indicators (7–9). However, there are few studies related to the outcomes after PCI, especially the reports on the long-term outcomes. In this study, a large single-center retrospective cohort study was conducted to investigate the predictive ability of Gensini score on clinical adverse outcomes 10 years in patients with CAD who underwent PCI.

METHODS

Study Design and Population

All patients were from the Clinical Outcomes and Risk Factors of Patients with Coronary Heart Disease after PCI (CORFCHD-PCI) study, which is a large single-center retrospective cohort study based on case data and follow-up records in the First Affiliated Hospital of Xinjiang Medical University. Design details have been registered at http://www.Chictr.org.cn (ID: ChiCTR-ORC-16010153). In brief, the CORFCHD-PCI study aims to evaluate and analyze the clinical outcomes and risk factors of patients with CAD after PCI. This cohort study included patients with CAD who underwent PCI at the First Affiliated Hospital of Xinjiang Medical University from January 2008 to December 2017. Demographic data, clinical characteristics, medical history, home medications, risk factors, blood samples, biochemical data, electrocardiogram data, echocardiography data, coronary angiography, and PCI procedures, and short-term and long-term outcomes were also collected. A total of 6,050 patients with CAD who underwent PCI in the CORFCHD-PCI study were evaluated initially. Three hundred and seventy-eight were excluded due to Gensini score data not being available or the presence of acute infections, malignancies, hepatobiliary disease, or blood disease. Finally, 5,672 patients were enrolled in this study, such as 2,110 patients with diabetes and 3,562 patients without diabetes. Diabetes was defined as either a previous diagnosis of diabetes treated with pharmacologic or non-pharmacologic measure, or new diabetes was defined according to the American Diabetes Association as the history of either presence of classic symptoms of diabetes with an unequivocal elevation of plasma glucose (2-h post-prandial or random of $\geq$200 mg/dl), fasting plasma glucose elevation on $\geq$126 mg/dl during hospitalization, or hemoglobin A1C $\geq$6.5% (48 mmol/mol) (10). Hypertension was defined as repeated (at least two times in different circumstances) blood pressure measurements $\geq$140/90 mmHg and was assumed to be present in patients taking anti-hypertensive drugs. Tobacco smoking was categorized based on the current smoking status (non-smoker or past smoker/current smoker), duration of smoking (non-smoker $<$20 years and $\geq$20 years), and the current number of cigarettes smoked per day (0 cigarettes per day, $<$20 cigarettes per day, and $\geq$20 cigarettes per day). Current and past smokers were defined as smokers and were compared to non-smokers. Alcohol drinking was evaluated by frequency ($<$1 time per week and $\geq$1 time per week) and by the amount of alcohol consumed at a time ($<$1 beer bottle and $\geq$1 beer bottle). Generally, a bottle of beer contains 4.5% of alcohol per 100 ml. Alcohol drinking was defined as alcohol consumption $\geq$1 time per week compared to alcohol consumption $<$1 time per week. **Figure 1** shows the flowchart of the inclusion and exclusion criteria used in the selection of participants. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. Because of the retrospective design of the study, the need to obtain informed consent from eligible patients was waived by the ethics committee.

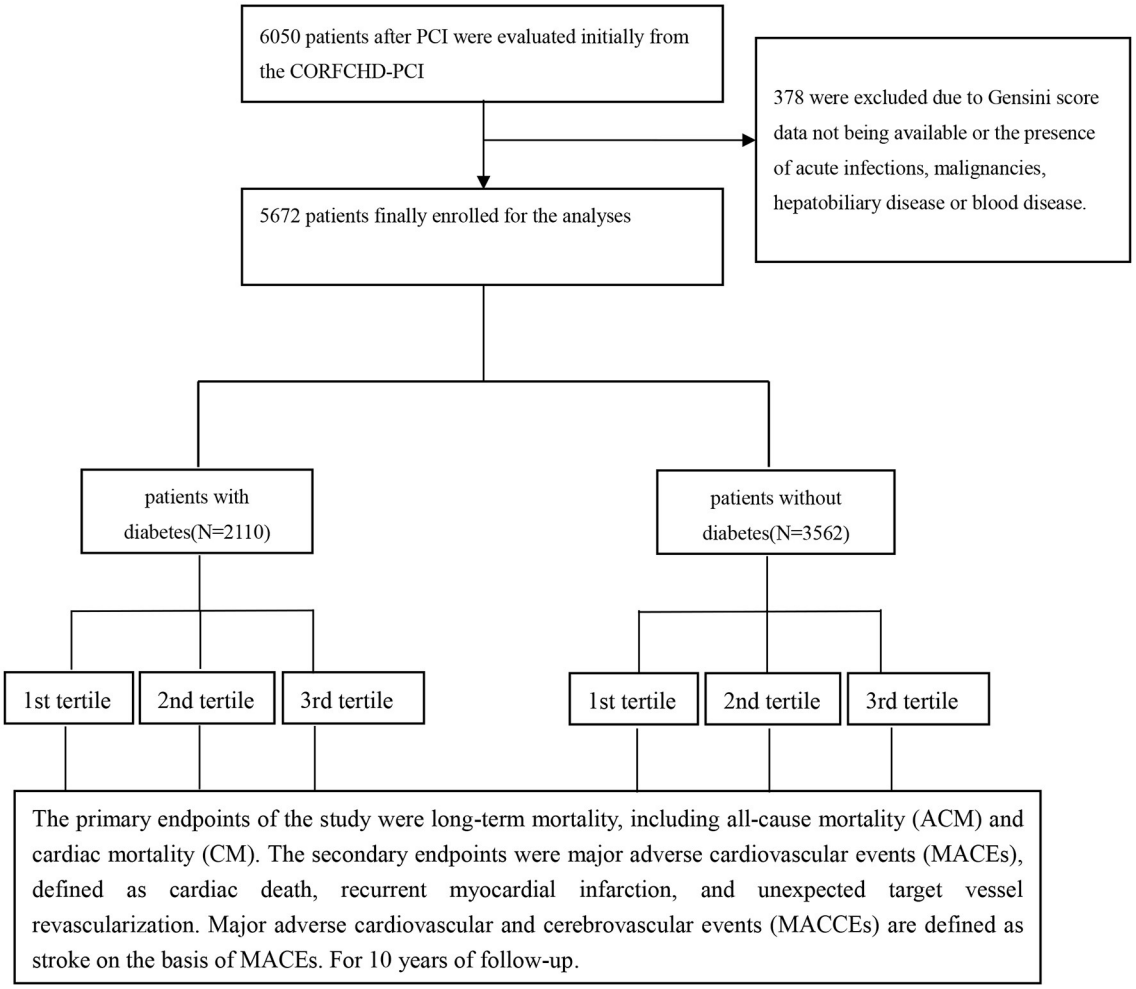

FIGURE 1 | The flowchart of participants' inclusion.

Assessment of Coronary Angiography

The coronary angiography was performed for all enrolled individuals, and the results were analyzed by at least two interventional physicians. The severity of CAD was evaluated by the Gensini score assessment system and scored by two independent senior cardiologists. The degree of stenosis and the coronary artery lesion site were scored as follows: 1 point for ≤25% narrowing, 2 points for 26–50% narrowing, 4 points for 51–75% narrowing, 8 points for 76–90% narrowing, 16 points for 91–99% narrowing, and 32 points for total occlusion. Thereafter, each lesion score is multiplied by a factor that takes into account the importance of the lesion's position in the coronary circulation (5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending coronary artery, 2.5 for the proximal segment of the circumflex artery, 1.5 for the mid-segment of the left anterior descending coronary artery, 1.0 for the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 for other segments). Finally, the Gensini score was calculated by summation of the individual coronary segment scores (4, 11). The patients were classified into three groups according to the tertile of Gensini score: first tertile (Gensini score <11 points), second tertile (Gensini score 11–38 points), third tertile (Gensini score >38 points).

Endpoints

The primary endpoints of the study were long-term mortality, such as all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were major adverse cardiovascular events (MACEs), defined as cardiac death, recurrent myocardial infarction (MI), and unexpected target vessel revascularization. Target vessel revascularization was defined as any repetitive revascularization in a treated vessel where there was stenosis of at least a 50% diameter in the presence of ischemic signs or symptoms or stenosis of at least 70% in the absence of

ischemic signs or symptoms. Major adverse cardiovascular and cerebrovascular events are defined as a stroke on the basis of MACEs.

Follow-Up

In our center, all of the patients who underwent PCI will receive regular follow-up after discharge at the end of 1 month, 3 months, 6 months, 1 year, 3 years, and 5 years. The follow-up was conducted by telephone contact, follow-up letter, or outpatient interviews. During the follow-up duration, an independent group of clinical physicians carefully checked and verified all events. To obtain high-quality data, before the study, we performed investigator training. All the questionnaire fillings were performed blindly, and the telephone recordings were performed in accordance with uniform criteria. The compliance of the drugs and adverse events were assessed at every visit for clinical follow-up. All the patients who underwent PCI were followed up for 31.0 (interquartile range, IQR: 30.0) months.

Statistical Analyses

The continuous data of normal distribution are presented as the mean ± SD, the differences between groups were compared by analysis of variance. If the difference between groups was statistically significant, further pairwise comparison was performed by the Fisher Least Significant Difference (LSD) method. The continuous data of non-normal distribution are presented as median (IQR), the differences between groups were compared by Kruskal-Wallis test or H-test. If the difference between groups was statistically significant, the Dunn method was further used for multiple comparisons. Categorical data are presented as the frequencies and percentages, the differences between groups were compared by the chi-square test. Based on the tertiles of Gensini score, the enrolled patients were classified into three groups: first tertile (Gensini score <11 points), second tertile (Gensini score 11–38 points), and third tertile (Gensini score >38 points). Kaplan-Meier analysis was used for cumulative incidence rates of long-term outcomes, and the log-rank test was used for comparisons between groups. Multivariable analysis was performed to assess the prognostic value of the Gensini score for adverse outcomes after adjusting for confounders. Hazard ratios (HRs) and 95% CIs were calculated. Interaction and stratified analyses were conducted according to DM status (with or without). All of the analyses were performed using SPSS22.0 for Windows statistical software (SPSS Inc., Chicago, IL, USA) and the statistical software packages R (The R Foundation; http://www.r-project.org; version 3.6.2). $p < 0.05$ was considered statistically significant for all comparisons.

RESULTS

Baseline Data

A total of 5,672 patients with CAD who underwent PCI, such as 2,110 patients with diabetes and 3,562 patients without diabetes, were divided into three groups according to Gensini score tertiles: first tertile (Gensini score <11 points; $n = 1{,}846$), second tertile (Gensini score 11–38 points; $n = 1{,}956$), third tertile (Gensini score >38 points; $n = 1{,}870$). As shown in **Table 1**, there are significant differences between the three groups for several variables, such as gender, age, smoking, family history of CAD, hypertension, and therapy with ARB or ACEI, SCr, and left ventricular ejection fraction (LVEF; all $p < 0.05$). In addition, several characteristics of lesions and some PCI parameters between these three groups show significant differences, such as LM, CTO, MVD, and number of diseased vessels, as shown in **Table 2**.

Clinical Outcomes

In the total population, during the median follow-up period of 31.0 (IQR: 30.0) months, there were 300 cases of ACM. In total, the incidence of ACM in the first tertile was 68 (3.7%), the second tertile was 90 (4.7%), and the third tertile was 142 (7.3%). There was a significant difference in the ACM incidence among these three groups ($p < 0.001$). We also found that CM occurred in 243 patients: 51 (2.8%) in the first tertile, 74 (3.9%) in the second tertile, 118 (6.1%) in the third tertile. There was a significant difference in the CM incidence among these three groups ($p < 0.001$). Regarding the incidence of MACEs and MACCEs, there are significant differences among the three groups (all $p < 0.001$). In the 3,562 CAD patients without diabetes and 2,110 CAD patients with diabetes, we found that there are significant differences among these three groups in the incidence of ACM, CM, MACEs, and MACCEs (all $p < 0.05$), as shown in **Table 3**. However, There were no significant differences among the groups in the incidence of stroke, readmission, recurrent MI, target vessel revascularization, and bleeding events (all $p > 0.05$), only in people with diabetes, the incidence of heart failure (HF) is statistically significant ($p = 0.035$; **Supplementary Table 1**).

Kaplan-Meier curves for Gensini score divided by tertiles and adverse outcomes are shown in **Figures 2–4**. In the total population, patients in the third tertile with Gensini score >38 points and the second tertile with Gensini scores 11–38 points showed significantly higher event rates for ACM (7.3 vs. 3.7% and 4.7 vs. 3.7%), CM (6.1 vs. 2.8% and 3.9 vs. 2.8%), MACEs (16.2 vs. 10.2% and 12.8 vs. 10.2%), and MACCEs (17.3 vs. 11.4% and 14.4 vs. 11.4%) compared with patients in the first tertile with Gensini score <11 points. These differences were also found in both patients without diabetes and patients with diabetes (data not shown).

Multivariate Cox Regression Analysis in Different Clinical Outcomes

Multivariable analysis was performed to assess the prognostic value of the Gensini score for adverse outcomes after adjusting for age, gender, smoking, family history of CAD, hypertension, SCr, LVEF, and therapy with ARB or ACEI. After multivariate Cox regression analyses, in the total population the respective risks of ACM, CM, MACEs, and MACCEs was increased 141.5% (HR = 2.415, 95% CI: 1.767–3.301, $p < 0.001$), 164.9% (HR = 2.649, 95% CI: 1.850–3.793, $p < 0.001$), 79.2% (HR = 1.792, 95% CI: 1.471–2.818, $p < 0.001$), and 76.3% (HR = 1.763, 95% CI: 1.460–2.129, $p < 0.001$) in the third tertile compare to those in the first tertile, as shown in **Table 4**. Cox regression stratified analysis shows that the correlation between Gensini score and the risk of ACM, CM,

TABLE 1 | Baseline characteristics of patients.

Variables	Gensini score			χ^2/F	*P*-value
	<11 points	11–38 points	>38 points		
CAD (*N* = 5,672)	***n* = 1,815**	***n* = 1,916**	***n* = 1,941**		
CCB, *n* (%)	234 (12.9)	214 (11.2)	207 (10.8)	4.762	0.092
β-Blockers, *n* (%)	706 (39.0)	793 (41.5)	801 (41.6)	3.224	0.199
ARB or ACEI, *n* (%)	374 (20.7)	430 (22.5)	491 (25.5)	12.390	**0.002**
Statins, *n* (%)	996 (55.3)	1,020 (53.7)	1,068 (55.6)	1.592	0.451
Smoking, *n* (%)	697 (38.4)	786 (41.0)	809 (41.7)	4.637	0.098
Drinking, *n* (%)	540 (29.8)	595 (31.1)	531 (28.6)	3.562	0.086
Family history of CAD, *n* (%)	192 (10.6)	244 (12.7)	279 (14.4)	12.309	**0.002**
Hypertension, *n* (%)	721 (39.7)	836 (43.6)	863 (44.5)	9.710	**0.008**
Age (years)	59.50 ± 10.74[a]	59.60 ± 10.86[a]	59.45 ± 10.99[a]	0.088	0.916
Gender, male, *n* (%)	1,286 (22.7)	1,515 (26.7)	1,426 (25.1)	19.664	**<0.001**
BUN (mmol/L)	5.48 ± 1.68[a]	5.52 ± 1.65[a]	5.55 ± 1.72[a]	0.783	0.457
SCr (μmol/L)	74.44 ± 21.98[a]	75.5 ± 18.55[a]	77.74 ± 20.31[b]	12.634	**<0.001**
TG (mmol/L)	1.90 ± 1.21[a]	1.91 ± 1.28[a]	1.90 ± 1.32[a]	0.046	0.955
TC (mmol/L)	3.93 ± 1.09[a]	3.97 ± 1.14[a]	3.97 ± 1.11[a]	0.819	0.441
HDL-C (mmol/L)	1.03 ± 0.52[a]	1.02 ± 0.44[a]	1.01 ± 0.44[a]	0.938	0.391
LDL-C (mmol/L)	2.45 ± 0.91[a]	2.47 ± 0.92[a]	2.45 ± 0.91[a]	0.360	0.698
ApoA1 (mmol/L)	1.17 ± 0.32[a]	1.17 ± 0.32[a]	1.16 ± 0.32[a]	0.383	0.682
ApoB (mmol/L)	0.84 ± 0.35[a]	0.86 ± 0.42[a]	0.85 ± 0.39[a]	1.510	0.221
Lp(a) (mmol/L)	217.99 ± 171.25[a]	223.04 ± 176.66[a]	220.11 ± 175.79[a]	0.369	0.692
LVEDD (mm)	49.94 ± 5.50[a]	50.16 ± 5.55[a]	49.89 ± 5.50[a]	1.135	0.321
LVEF (%)	61.30 ± 6.84[a]	60.9 ± 7.08[a]	60.94 ± 7.22[a]	1.919	0.147
CAD without diabetes (*N* = 3,562)	***n* = 1,251**	***n* = 1,208**	***n* = 1,103**		
CCB, *n* (%)	166 (13.3)	132 (11.0)	120 (11.6)	4.185	0.123
β-Blockers, *n* (%)	482 (38.7)	502 (41.7)	458 (41.8)	3.234	0.199
ARB or ACEI, *n* (%)	255 (20.5)	260 (21.6)	279 (25.5)	9.106	**0.011**
Statins, *n* (%)	685 (55.2)	633 (52.8)	594 (54.3)	1.452	0.484
Smoking, *n* (%)	477 (38.1)	506 (41.9)	485 (44.0)	8.599	**0.014**
Drinking, *n* (%)	374 (29.9)	385 (31.9)	307 (27.8)	4.483	0.106
Family history of CAD, *n* (%)	121 (9.7)	150 (12.4)	160 (14.5)	13.050	**0.001**
Hypertension, *n* (%)	439 (35.1)	484 (40.1)	441 (40.0)	8.364	**0.015**
Age (years)	59.16 ± 10.83[a]	59.17 ± 11.06[a]	58.83 ± 11.16[a]	0.350	0.704
Gender, male, *n* (%)	1,009 (23.5)	1,170 (27.2)	1,066 (24.8)	28.309	**<0.001**
BUN (mmol/L)	5.45 ± 1.61[a]	5.52 ± 1.61[a]	5.43 ± 1.60[a]	1.125	0.325
SCr (μmol/L)	73.76 ± 20.74[a]	75.66 ± 18.14[b]	77.52 ± 17.92[c]	11.092	**<0.001**
TG (mmol/L)	1.80 ± 1.06[a]	1.84 ± 1.21[a]	1.76 ± 1.03[a]	1.404	0.246
TC (mmol/L)	3.87 ± 1.06[a]	3.93 ± 1.12[a]	3.91 ± 1.05[a]	0.875	0.417
HDL-C (mmol/L)	1.03 ± 0.56[a]	1.0150 ± 0.44[a]	1.01 ± 0.46[a]	0.684	0.505
LDL-C (mmol/L)	2.43 ± 0.92[a]	2.45 ± 0.92[a]	2.44 ± 0.89[a]	0.158	0.854
ApoA1 (mmol/L)	1.15 ± 0.30[a]	1.17 ± 0.34[a]	1.16 ± 0.34[a]	1.031	0.357
ApoB (mmol/L)	0.82 ± 0.34[a]	0.85 ± 0.43[a]	0.84 ± 0.39[a]	1.631	0.196
LP(a) (mmol/L)	219.92 ± 167.47[a]	226.87 ± 177.35[a]	218.28 ± 171.35[a]	0.767	0.465
LVEDD (mm)	50.07 ± 5.68[a]	50.12 ± 5.63[a]	49.88 ± 5.57[a]	0.528	0.590
LVEF (%)	61.18 ± 7.01[a]	60.99 ± 7.18[a]	61.01 ± 7.32[a]	0.235	0.790
CAD with diabetes (*N* = 2,110)	***n* = 564**	***n* = 708**	***n* = 838**		
CCB, *n* (%)	68 (12.1)	82 (11.6)	87 (10.5)	1.038	0.595
β-Blockers, *n* (%)	224 (39.9)	291 (41.2)	343 (41.2)	0.317	0.853
ARB or ACEI, *n* (%)	119 (21.2)	170 (24.2)	212 (25.5)	3.470	0.176
Statins, *n* (%)	311 (55.6)	387 (55.3)	474 (57.2)	0.677	0.713

(Continued)

TABLE 1 | Continued

Variables	Gensini score			χ^2/F	*P*-value
	<11 points	11–38 points	>38 points		
Smoking, *n* (%)	220 (39.0)	280 (39.5)	324 (38.7)	0.127	0.939
Drinking, *n* (%)	166 (29.4)	210 (29.7)	218 (26.0)	3.148	0.207
Family history of CAD, *n* (%)	71 (12.6)	94 (13.3)	119 (14.2)	0.782	0.676
Hypertension, *n* (%)	282 (50.0)	352 (49.7)	422 (50.4)	0.064	0.969
Age (years)	60.28 ± 10.51[a]	60.32 ± 10.49[a]	60.26 ± 10.70[a]	0.006	0.994
Gender, male, *n* (%)	277 (20.2)	345 (25.1)	360 (26.2)	0.908	0.635
BUN (mmol/L)	5.54 ± 1.82[a]	5.51 ± 1.71[a]	5.71 ± 1.86[a]	2.701	0.067
SCr (μmol/L)	75.91 ± 24.40[ab]	75.27 ± 19.23[b]	78.01 ± 23.04[c]	3.181	**0.042**
TG (mmol/L)	2.10 ± 1.46[a]	2.03 ± 1.39[a]	2.09 ± 1.59[a]	0.384	0.681
TC (mmol/L)	4.05 ± 1.13[a]	4.04 ± 1.16[a]	4.04 ± 1.17[a]	0.004	0.996
HDL-C (mmol/L)	1.02 ± 0.43[a]	1.02 ± 0.42[a]	1.01 ± 0.43[a]	0.287	0.750
LDL-C (mmol/L)	2.49 ± 0.88[a]	2.51 ± 0.91[a]	2.47 ± 0.93[a]	0.360	0.698
ApoA1 (mmol/L)	1.19 ± 0.35[a]	1.16 ± 0.28[a]	1.16 ± 0.28[a]	2.827	0.059
ApoB (mmol/L)	0.89 ± 0.38[a]	0.88 ± 0.42[a]	0.87 ± 0.39[a]	0.473	0.623
LP(a) (mmol/L)	213.97 ± 179.00[a]	216.74 ± 175.47[a]	222.45 ± 181.39[a]	0.405	0.667
LVEDD (mm)	49.63 ± 5.08[a]	50.22 ± 5.41[a]	49.91 ± 5.41[a]	1.670	0.189
LVEF (%)	61.69 ± 6.45[a]	60.76 ± 6.90[b]	60.85 ± 7.09[bc]	3.055	**0.047**

[a,b,c]*After comparing the means between groups, the test was performed. If there are the same letters between the groups, the difference is not statistically significant (P > 0.05); if the letters are different between the groups, the difference is statistically significant (P < 0.05). TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein a; Scr, serum creatinine; BUN, blood urea nitrogen; ACEI, angiotensin-converting enzyme inhibitor ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection function. In order to make the number of patients in different groups more clearly visible.*

TABLE 2 | Procedural characteristics of patients in the total population.

Variables	Gensini score			X^2/F	*P*-value
	<11 points *n* = 1,815	11–38 points *n* = 1,916	>38 points *n* = 1,941		
LM, *n* (%)	78 (4.3)	128 (6.7)	205 (10.6)	56.075	**<0.0001**
CTO, *n* (%)	249 (13.7)	321 (16.8)	788 (40.6)	453.960	**<0.0001**
MVD, *n* (%)	889 (49.0)	1,346 (70.3)	1,522 (78.4)	383.333	**<0.0001**
DES, *n* (%)	1,723 (95.0)	1,800 (93.9)	1,831 (94.3)	1.935	0.380
Pre-expansion, *n* (%)	1,593 (87.8)	1,645 (85.9)	1,675 (86.3)	3.386	0.184
Post-expansion, *n* (%)	1,140 (62.8)	1,194 (62.3)	1,216 (62.6)	0.114	0.945
Number of stents	1.043 ± 0.210[a]	1.043 ± 0.227[a]	1.038 ± 0.216[a]	0.376	0.689
Number of diseased vessels	1.716 ± 0.810[a]	2.065 ± 0.809[b]	2.305 ± 0.802[c]	251.493	**<0.0001**
Diameter of stents, (mm)	2.857 ± 0.369[a]	2.832 ± 0.366[b]	2.861 ± 0.386[ac]	3.529	0.029
Length of stents, (mm)	28.193 ± 6.958[a]	27.745 ± 7.011[a]	28.084 ± 6.860[a]	2.131	0.119
Expansion pressure, (atm)	11.855 ± 3.407[a]	11.793 ± 2.486[a]	11.899 ± 2.565[a]	0.322	0.725

[a,b,c]*After comparing the means between groups, the test was performed. If there are the same letters between the groups, the difference is not statistically significant (P > 0.05); if the letters are different between the groups, the difference is statistically significant (P < 0.05). LM, left main coronary artery disease; CTO, chronic total occlusion coronary artery disease; MVD, multivessel disease; DES, drug-eluting stent; pre-expansion, before the stent is implanted, the pressure of the balloon is used to expand the coronary artery stenosis; post-expansion, after the stent is implanted, the pressure of the balloon is used to fully expand the stent. In order to make the number of patients in different groups more clearly visible.*

MACE, MACCE was statistically significant in the diabetic status (with or without) (all interactions $p < 0.05$). In the population with diabetes, compared with the first tertile, the risks of ACM were increased 248.5% (HR = 3.485, 95% CI: 1.973–6.154, $p < 0.001$) in the third tertile and 69.0% (HR = 1.690, 95% CI: 0.904–3.161, $p < 0.001$) in second tertile. In the population without diabetes, compared with the first tertile, the risks of ACM were increased 89.9% (HR = 1.899, 95% CI: 1.285–2.807, $p = 0.001$) in the third tertile and 28.4% (HR = 1.284, 95% CI: 0.855–1.928, $p = 0.229$) in second tertile. The results of the interaction test showed that the relationship between Gensini score and ACM was different in diabetes status (with or without) ($p = 0.011$).

TABLE 3 | Clinical outcomes and Gensini score according to tertiles.

Clinical outcomes	Gensini score			X^2	*P*-value
	<11 points	11–38 points	>38 points		
CAD (*N* = 5,672)	***n* = 1,815**	***n* = 1,916**	***n* = 1,941**		
ACM	68 (3.7)	90 (4.7)	142 (7.3)	25.877	<0.001
CM	51 (2.8)	74 (3.9)	118 (6.1)	25.706	<0.001
MACEs	185 (10.2)	246 (12.8)	315 (16.2)	30.164	<0.001
MACCEs	207 (11.4)	275 (14.4)	336 (17.3)	26.517	<0.001
CAD without diabetes (*N* = 3,562)	***n* = 1,251**	***n* = 1,208**	***n* = 1,103**		
ACM	53 (4.2)	59 (4.9)	71 (6.4)	6.064	0.048
CM	40 (3.2)	49 (4.1)	60 (5.4)	7.426	0.024
MACEs	131 (10.5)	150 (12.4)	164 (14.9)	10.376	0.006
MACCEs	146 (11.7)	165 (13.7)	177(16.0)	9.499	0.009
CAD with diabetes (*N* = 2,110)	***n* = 564**	***n* = 708**	***n* = 838**		
ACM	15 (2.7)	31 (4.4)	71 (8.5)	24.517	<0.001
CM	11 (2.0)	25 (3.5)	58 (6.9)	21.707	<0.001
MACEs	54 (9.6)	96 (13.6)	151 (18.0)	20.090	<0.001
MACCEs	61 (10.8)	110 (15.5)	159 (19.0)	17.014	<0.001

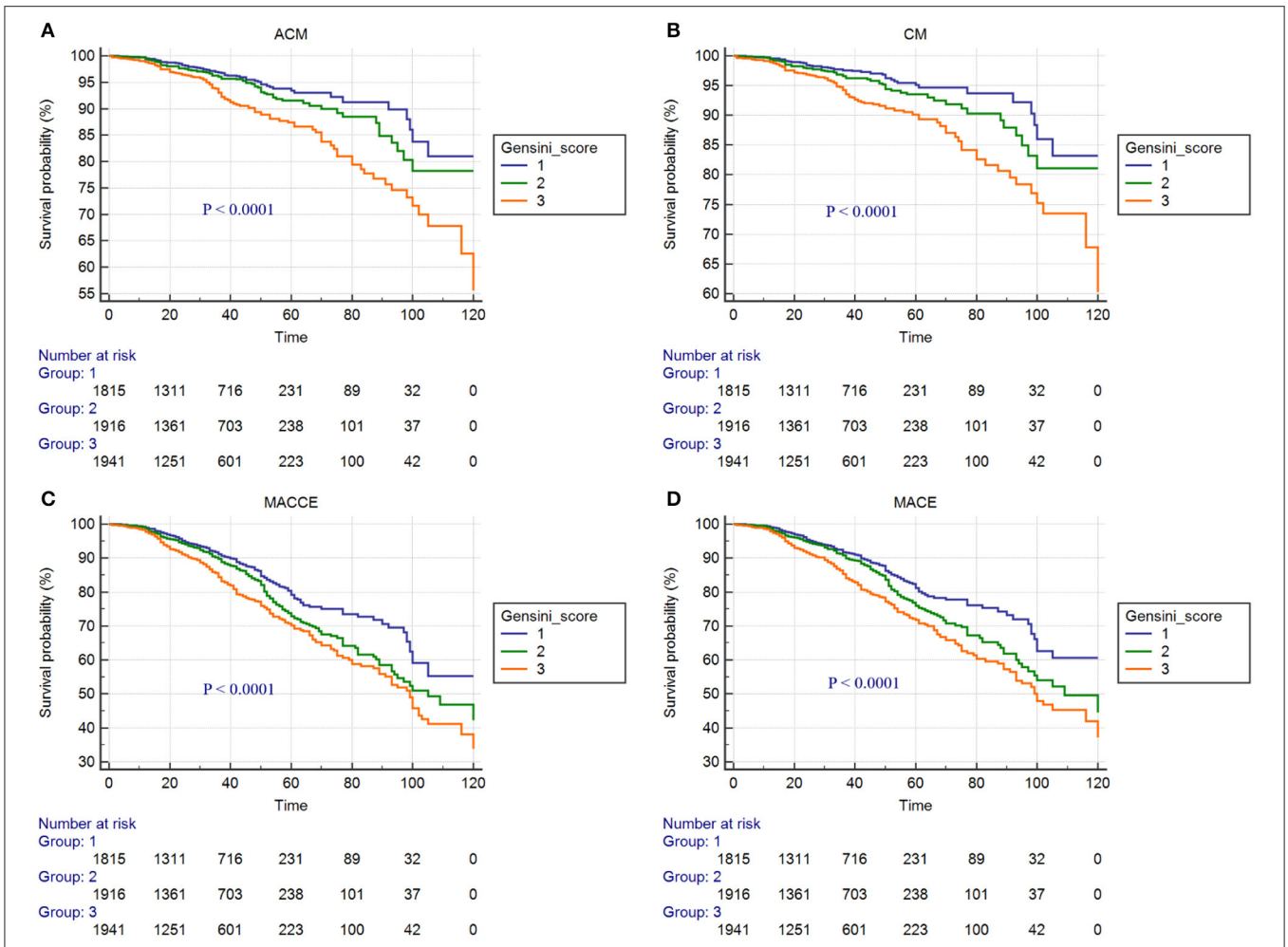

FIGURE 2 | Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of primary endpoints and secondary endpoints: **(A)** ACM; **(B)** CM; **(C)** MACCEs; **(D)** MACEs. (In the total population).

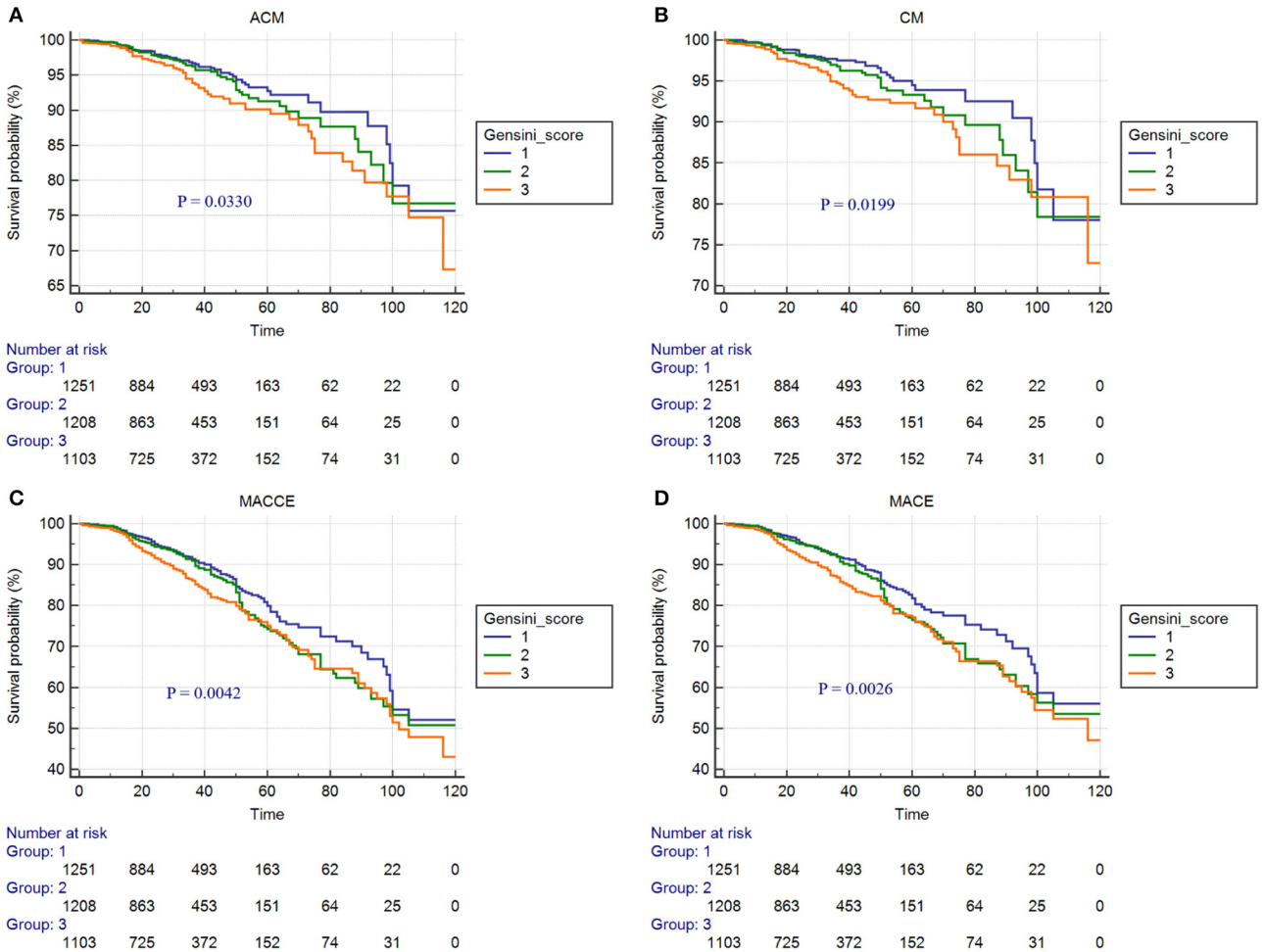

FIGURE 3 | Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of primary endpoints and secondary endpoints: **(A)** ACM; **(B)** CM; **(C)** MACCEs; **(D)** MACEs. (In the 3,562 CAD patients without diabetes).

Compared with non-diabetic people, the higher the Gensini score in diabetic people, the higher the risk of ACM. These differences are also found in other clinical outcomes (CM, MACEs, and MACCEs) (data not shown), as shown in **Table 5**. In addition, compared with the non-diabetic population, the incidence of ACS was higher in the diabetic population, and the difference was statistically significant ($p = 0.002$; **Supplementary Table 2**).

DISCUSSION

In the present study, we demonstrate that Gensini score in patients with CAD treated with PCI was an independent predictor of adverse outcomes over up to 10 years of follow-up. The present results indicate the strong relationship between Gensini score and adverse outcomes over a follow-up period of up to 10 years in patients with CAD who underwent PCI. Recent research performed by Yokokawa et al. (11) reported that a high Gensini score after PCI was associated with higher CM in HF patients, suggesting that residual coronary atherosclerotic burden might lead to a higher risk of cardiac events. In our study, we enrolled 5,672 patients with CAD who underwent PCI and analyzed four different clinical outcomes: ACM, CM, MACEs, MACCEs, and further verified that the Gensini score was an independent predictor of adverse outcomes of patients with CAD after PCI. The present results were compatible with those of some previous studies. A study by Reynolds et al. (12) investigated that CAD severity was a highly significant predictor of ACM, MI, CV death, and other five adverse clinical outcomes, independent of ischemia severity and other clinical predictors.

The main purpose of coronary angiography is to determine whether there is CAD, assess the degree of coronary artery stenosis, and treat diseased vessels. The morphology and degree of stenosis of coronary artery lesions determine the choice of the treatment plan. At present, there are many scoring systems for quantitative analysis of coronary artery lesions, among which the Gensini score and SYNTAX score are more commonly used. They have different emphases, and each has its own

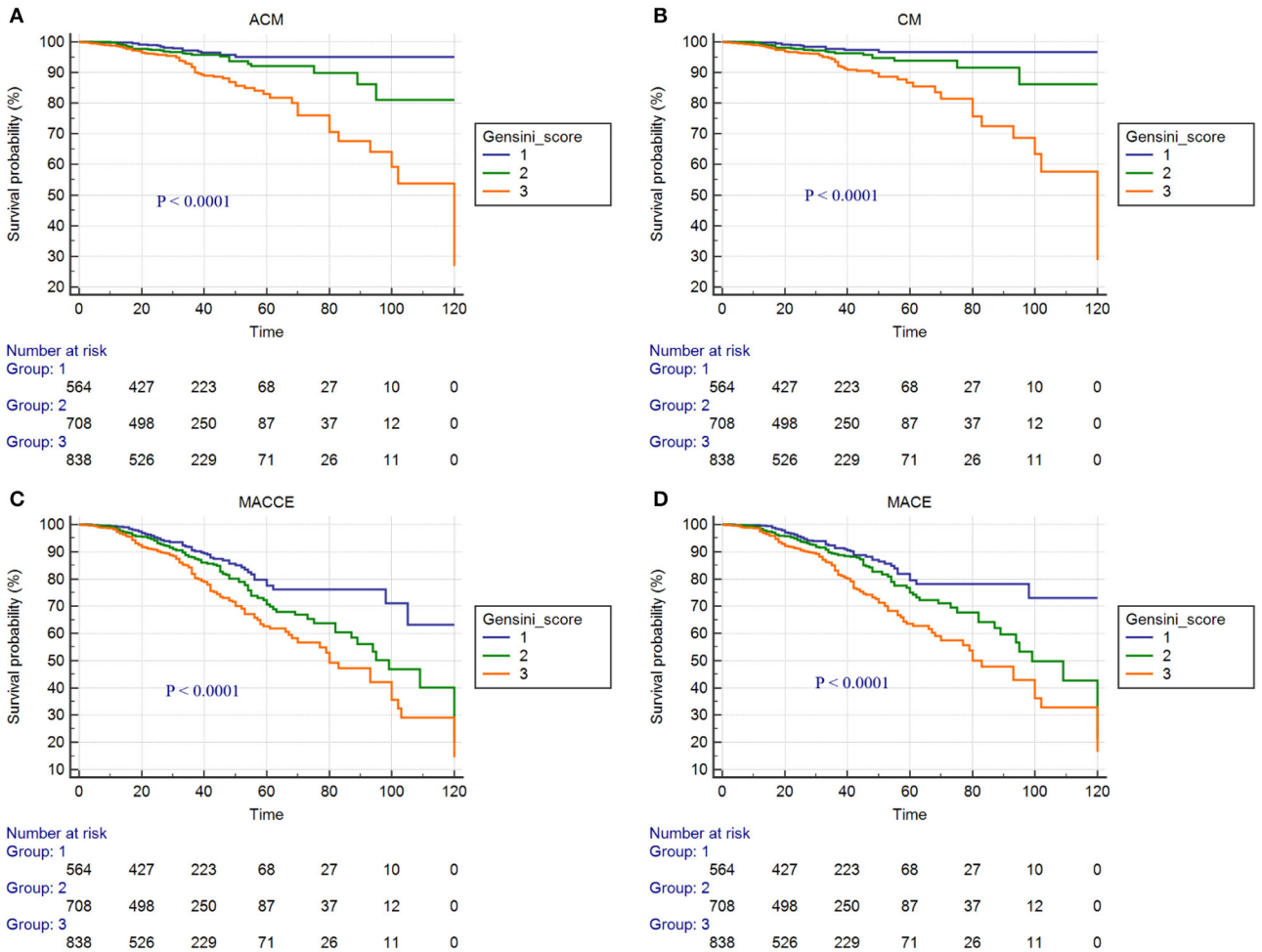

FIGURE 4 | Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of primary endpoints and secondary endpoints: **(A)** ACM; **(B)** CM; **(C)** MACCEs; **(D)** MACEs. (In the 2,110 CAD patients with diabetes).

advantages and disadvantages (13). Gensini score fully considers the number, location, and degree of coronary artery lesions and is a relatively scientific evaluation standard. The scoring system divides the coronary artery into 14 segments, each of which has its own weighting coefficient. In particular, the left main artery, the proximal and middle segments of the left anterior descending branch dominate the blood supply to the left ventricle, so they have a higher weighting coefficient (14). At the same time, the Gensini score has been widely integrated into various clinical studies. Currently, the most reported research is Gensini score combined with certain biochemical indicators to assess the severity of CAD and predict long-term outcomes. A study by Duran et al. suggested that serum uric acid levels were positively correlated with the Gensini scores in patients with the acute coronary syndrome (ACS). The higher the serum uric acid level, the greater the number of coronary artery lesions, the more severe the stenosis, and even total occlusion. Multivariate analysis showed that serum uric acid level was an independent risk factor for multivessel disease (7). Another study by Chen et al. investigated that the neutrophil-to-lymphocyte ratio (NLR) was an independent predictor of high Gensini score, and NLR was positively correlated with Gensini score. In the ROC curves analysis, the NLR was found to have the largest area under the curve (AUC = 0.63, 95% CI: 0.59–0.67, $p = 0.000$), with an optimal cut-off value of 2.04 (sensitivity: 62.1%, specificity: 54.8%) for predicting a high Gensini score (8). Research performed by Liu et al. reported that the incidence of MACEs in patients with STEMI within 6 months after emergency PCI was 19.36%. Compared with the non-MACEs group, the mean platelet volume (MPV) and Gensini score of the MACEs group were significantly higher. Multivariate Cox analysis showed that MPV and Gensini score were independent risk factors for MACEs in patients with STEMI after emergency PCI (9).

The SYNTAX score is also a commonly used method for quantitative analysis of coronary artery lesions. The scoring

TABLE 4 | Multivariable Cox regression analysis of ACM, CM, MACEs, and MACCEs.

Variables	Total population (ACM)			Total population (CM)			Total population (MACEs)			Total population (MACCEs)		
	Z-values	*P*-values	HR (95%CI)	*Z*-values	*P*-values	HR (95%CI)	*Z*-values	*P*-values	HR (95%CI)	*Z*-values	*P*-values	HR (95%CI)
Gender, male	0.018	0.894	1.022 (0.747–1.397)	0.138	0.710	1.069 (0.753–1.516)	1.014	0.314	0.898 (0.728–1.107)	1.790	0.181	0.873 (0.715–1.065)
Age	12.331	<0.001	1.022 (1.010–1.035)	3.555	0.059	1.013 (0.999–1.027)	0.142	0.706	0.999 (0.991–1.006)	0.113	0.737	1.001 (0.994–1.009)
Smoking	0.996	0.318	0.868 (0.657–1.146)	2.550	0.110	0.774 (0.565–1.060)	6.347	0.012	0.797 (0.667–0.951)	9.765	0.002	0.763 (0.644–0.904)
Family history of CAD	3.601	0.058	0.591 (0.343–1.017)	1.814	0.178	0.677 (0.384–1.194)	2.053	0.152	1.201 (0.935–1.541)	2.216	0.137	1.200 (0.944–1.526)
Hypertension	5.349	0.021	1.341 (1.046–1.720)	3.045	0.081	1.285 (0.970–1.702)	12.867	<0.001	1.341 (1.142–1.574)	14.607	<0.001	1.348 (1.157–1.571)
ARB or ACEI	36.213	<0.001	0.099 (0.047–0.211)	28.900	<0.001	0.126 (0.059–0.268)	0.908	0.341	0.910 (0.748–1.105)	0.753	0.386	0.921 (0.765–1.109)
SCr	5.569	0.018	1.006 (1.001–1.011)	9.670	0.002	1.008 (1.003–1.013)	0.631	0.427	1.002 (0.998–1.005)	1.321	0.250	1.002 (0.999–1.006)
LVEF	0.585	0.444	1.007 (0.990–1.024)	0.001	0.981	1.000 (0.982–1.019)	0.191	0.662	1.002(0.991–1.014)	1.168	0.280	1.006 (0.995–1.017)
Gensin score (<11 points as reference)												
11–38 points	3.809	0.051	1.400 (0.999–1.963)	4.383	0.036	1.515 (1.027–2.234)	3.916	0.048	1.232 (1.002–1.516)	5.740	0.017	1.272 (1.045–1.549)
>38 points	30.611	<0.001	2.415 (1.767–3.301)	28.284	<0.001	2.649 (1.850–3.793)	33.822	<0.001	1.792 (1.472–2.181)	34.717	<0.001	1.763 (1.460–2.129)

SCr, serum creatinine; ACEI, angiotensin-converting enzyme inhibitor ARB, angiotensin receptor blocker; LVEF, left ventricular ejection function.

method uses the 16-segment method, combining the dominant distribution, lesion location, degree of stenosis, and lesion characteristics to score coronary artery lesions with a diameter of ≥1.5 mm and a degree of stenosis ≥50%. The scoring system refines the following four aspects: dominant distribution, number of lesions, number of diseased vascular segments, and lesion characteristics, mainly including chronic total occlusion lesions, bifurcation lesions, opening lesions, severe tortuosity lesions, >20 mm lesions, calcification lesions, thrombosis lesions, and small vessel lesions (15). The higher the SYNTAX score, the more severe the coronary artery lesions, the worse the prognosis, and the higher the revascularization rate. The SYNTAX score can assist in guiding the choice of reasonable revascularization in patients with three branches lesions or left main artery lesions. The higher the SYNTAX score, the worse the short-term clinical outcome after PCI (16, 17). Wang reported that a study of 2,348 patients with congenital heart disease (CHD) and the SYNTAX score were performed for all enrolled patients before PCI, and then divided into high-risk group, medium-risk group, and low-risk group. The results showed that the differences in ACM and MACEs among the three groups were statistically significant. Multivariate Cox regression analysis showed that SYNTAX score was a risk factor for poor prognosis in patients with CHD after PCI (18).

However, in actual clinical work, the left main artery lesions only account for 3–5%, and the multivessel lesions only account for about 12%. The majority of cases with clear indications for coronary intervention are type A or type B lesions. Therefore, it is complicated and cumbersome to carry out quantitative analysis of coronary artery lesions using SYNTAX score regularly. Because of its simplicity and science, the Gensini score is suitable for the majority of patients with CAD, especially for UA, NSTEMI, and STEMI patients who underwent emergency PCI treatment. It can quickly evaluate coronary artery lesions, identify high-risk patients, and promptly carry out diagnosis and treatment.

In our study, there were significant differences in the incidence of ACM, CM, MACEs, and MACCEs among the three Gensini score groups in patients with CAD who underwent PCI with or without diabetes. Kaplan-Meier curve showed that in the clinical adverse outcomes of ACM, CM, MACEs, and MACEs, the prognosis of patients in the low Gensini score group was better than those in the intermediate Gensini score group and high Gensini score group. After multivariate Cox regression analyses, the risks of ACM, CM, MACEs, and MACCEs increased significantly in the third tertile compared with those in the first tertile, and this result was more pronounced in patients with diabetes. The above results show that, first of all, the higher the Gensini score of patients with CAD after PCI, the greater risk of poor clinical outcomes. Therefore, patients with high Gensini score should be closely followed up and timely adjusted treatment to avoid the occurrence of poor prognosis. Secondly, the risk of adverse prognosis was significantly higher in diabetic patients than in non-diabetic patients. Some previous studies have also proved this point of view. The study of Karayiannides and Norhammar believed that patients with diabetes had higher rates

TABLE 5 | Cox regression stratified analysis of Gensini score and the risk of ACM, CM, MACEs, MACCEs.

Clinical outcomes/factors		Gensini score HR (95%CI)			Interaction *P*-value
		<11 points	11–38 points	>38 points	
ACM					
Diabetes	With	1	1.690 (0.904–3.161)	3.485 (1.973–6.154)	0.011
	Without	1	1.284 (0.855–1.928)	1.899 (1.285–2.807)	
CM					
Diabetes	With	1	1.817 (0.882–3.744)	3.604 (1.866–6.963)	0.007
	Without	1	1.401 (0.879–2.236)	2.151 (1.378–3.365)	
MACEs					
Diabetes	With	1	1.535 (1.076–2.189)	2.302 (1.649–3.215)	0.008
	Without	1	1.068 (0.824–1.384)	1.481 (1.152–1.904)	
MACCEs					
Diabetes	With	1	1.598 (1.145–2.231)	2.198 (1.600–3.018)	0.010
	Without	1	1.095 (0.854–1.403)	1.498 (1.176–1.907)	

Multivariable analysis was performed to assess the prognostic value of Gensini score for adverse outcomes after adjusting for age, gender, smoking, family history of CAD, hypertension, Scr, and LVEF, as well as therapy with ARB or ACEI.

of ACM (9.0 vs. 4.9%; $p < 0.001$) when compared with patients without diabetes. Multivariable regression analysis showed that diabetes was independently associated with increased risk for ACM at 1 year (HR = 1.57; 95% CI: 1.23–2.00; $p < 0.001$) (19). In addition, a multicenter cohort study in South Korea showed that the presence of diabetes and renal failure were strong predictors of MACE and target-vessel revascularization (TVR). After inverse probability of treatment weighting (IPTW) analyses, patients with diabetes had significantly increased rates of 2-year MACE (HR = 2.07, 95% CI: 1.50–2.86; $p < 0.001$) (10). A probable explanation is that patients with diabetes had more CV risk factors than patients without diabetes, some patients with adverse prognoses most likely have a more advanced diabetes disease with longer duration, worse glycemic control, higher risk for hypoglycemia, and underlying macro- and microvascular complications. Finally, our research concluded that age, smoking, hypertension, ARB or ACEI drugs, and Scr were also independent predictors of ACM, CM, MACEs, and MACCEs. It suggests that smoking cessation, blood pressure control, regular use of ARB or ACEI drugs, and protection of renal function have positive effects on improving the long-term prognosis of patients with CAD who underwent PCI. There were several strengths of our study. First, this study is a large single-center retrospective cohort study involving a total of 5,672 patients with CAD who underwent PCI, which improved the statistical power. Second, all patients have undergone long-term follow-up, with the longest experience being 10 years. Compared with previous studies, the follow-up time is the longest. Finally, we analyzed the data with multifaceted methods and provided a comprehensive understanding of the relationship between the Gensini score and clinical outcomes. However, the limitations of our study are also mentioned. The present study is a single-center retrospective cohort design. Therefore, our results need to be further verified by a multicenter, prospective study.

CONCLUSION

In conclusion, the present study suggests that the Gensini score is an independent predictor of long-term adverse outcomes in patients with CAD who underwent PCI, and it has a stronger predictive value in the diabetic population. Our results emphasize that patients with high Gensini scores should be closely followed up and timely adjustment of treatment to avoid adverse clinical outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

K-YW contributed to the literature search, study design, data collection, data analysis and interpretation, and writing of the manuscript. T-TW, Y-YZ, and XX participated in the literature search, study design, data analysis and interpretation, and in the writing of the manuscript. Y-TM conducted the literature search, data analysis and interpretation, and wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.778615/full#supplementary-material

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