CONTEMPORARY REVIEW

Therapeutic Management of Anomalous Coronary Arteries Originating From the Opposite Sinus of Valsalva: Current Evidence, Proposed Approach, and the Unknowing

Marius Reto Bigler MD, PhD; Alexander Kadner MD; Lorenz Räber MD, PhD; Afreed Ashraf, BMed; Stephan Windecker MD; Matthias Siepe MD; Massimo Antonio Padalino MD, PhD; Christoph Gräni MD, PhD

ABSTRACT: Anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS) are a challenge because of their various anatomic and clinical presentation. Although the prevalence is low, the absolute numbers of detected ACAOS are increasing because of the growing use of noninvasive anatomical imaging for ruling out coronary artery disease. As evidence-based guidelines are lacking, treating physicians are left in uncertainty for the optimal management of such patients. The sole presence of ACAOS does not justify surgical correction, and therefore a thorough anatomic and hemodynamic assessment is warranted. Invasive and noninvasive multimodality imaging provides information to the clinical question whether the presence of ACAOS is an innocent coincidental finding, is responsible for the patient’s symptoms, or even might be a risk for sudden cardiac death. Based on recent clinical data, focusing on the pathophysiology of patients with ACAOS, myocardial ischemia is dependent on both the extent of fixed and dynamic components, represented by anatomic high-risk features. These varying combinations should be considered individually in the decision making for the different therapeutic options. This state-of-the-art review focuses on the advantages and limitations of the common contemporary surgical, interventional, and medical therapy with regard to the anatomy and pathophysiology of ACAOS. Further, we propose a therapeutic management algorithm based on current evidence on multimodality invasive and noninvasive imaging findings and highlight remaining gaps of knowledge.

Key Words: ACAOS ■ anomalous coronary artery originating from the opposite sinus of Valsalva ■ PCI ■ coronary unroofing ■ L-ACAOS ■ R-ACAOS

According to the US and European guidelines with the growing use of recommended noninvasive imaging for the evaluation of coronary artery disease (CAD) in chronic coronary syndromes,1 an increase in absolute number of newly detected coronary artery anomalies is expected.2,3 Of particular interest are anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS). There exist different clinical presentations and anatomic variants of ACAOS. Anomalous courses of the ectopic proximal anomalous coronary artery include prepulmonic (anterior of the pulmonary artery), intraseptal (also called subpulmonic course, with a deep course under the pulmonary artery), retroaortic (behind the aorta), and interarterial (between the great vessels, ie, aorta and pulmonary artery).4 Most of these variants are considered benign and coincidental findings with no hemodynamic relevance and thus not related to cardiac

Correspondence to: Christoph Gräni, MD, PhD, FESC, FACC, FSCCT, FSCMR, Department of Cardiology University Hospital Bern, Freiburgstrasse 18, 3010 Bern, Switzerland. Email: christoph.graeni@insel.ch

For Sources of Funding and Disclosures, see page 16.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAH is available at: www.ahajournals.org/journal/jaha
is limited,17–21 and treating physicians are often left in therapeutic approaches in patients with these anomalies and European guidelines about diagnostic and therapeutic management options for ACAOS.15,16,22 The pathophysiology of ACAOS, the underlying mechanisms of ischemia remain ambiguous because of the highly variable extent of the different anatomic high-risk features.22 The interarterial course was historically considered to be main driver of ischemia, assuming a scissor-like interruption of the coronary blood flow, especially during exertion, as a consequence of the close proximity of the anomalous segment to the aorta and pulmonary artery.5 However, 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 higher-pressure anomalous coronary artery. On the contrary, at the site of closest aortopulmonary proximity, the anomalous segment frequently runs inside the aortic wall with associated other anatomic high-risk features.6,24,25 Therefore, the interarterial course may rather act as a surrogate for the anatomic high-risk features such as the slitlike ostium, the acute take-off angle, the proximal narrowing (also referred to as hypoplasia) with elliptic vessel shape, and, most importantly, the intramural course (ie, course within the tunica media of the aortic wall).25–36 In the 2-tier concept, hemodynamic relevance of the fixed components is featured by the slitlike ostium and proximal narrowing, while the dynamic component is represented by the acute take-off angle, elliptic vessel shape, and, most importantly, the intramural course. Elements of the fixed component correspond best to the concept of obstructive coronary stenosis known from CAD, that is, flow restrictions based on the static reduction of the cross-sectional area. Accordingly, assessment can be performed similarly to patients with CAD, including determination of percentage of cross-sectional area stenosis of the anomalous in relation to the unobstructed, distal reference segment,37 or measurement of the pressure gradient over the anomalous segment, that is, fractional flow reserve (FFR) or noninvasive ischemia testing using adenosine as a pharmacologic vasodilator.38 Revascularization may then be selected to correct all components and to eliminate the hemodynamic relevance of the anomalous coronary artery. This state-of-the-art review focuses on the advantages and limitations of the common contemporary surgical, interventional, and medical therapy with regard to the anatomy and pathophysiology of ACAOS. Further, we propose a therapeutic management algorithm based on current evidence on multimodality invasive and noninvasive imaging findings and highlight remaining gaps of knowledge.

PATHOPHYSIOLOGICAL MECHANISMS OF ISCHEMIA IN ACAOS

Despite growing understanding of the pathophysiology of ACAOS, the underlying mechanisms of ischemia remain ambiguous because of the highly variable extent of the different anatomic high-risk features.22 The interarterial course was historically considered to be main driver of ischemia, assuming a scissor-like interruption of the coronary blood flow, especially during exertion, as a consequence of the close proximity of the anomalous segment to the aorta and pulmonary artery.5 However, 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 higher-pressure anomalous coronary artery. On the contrary, at the site of closest aortopulmonary proximity, the anomalous segment frequently runs inside the aortic wall with associated other anatomic high-risk features.6,24,25 Therefore, the interarterial course may rather act as a surrogate for the anatomic high-risk features such as the slitlike ostium, the acute take-off angle, the proximal narrowing (also referred to as hypoplasia) with elliptic vessel shape, and, most importantly, the intramural course (ie, course within the tunica media of the aortic wall).25–36 In the 2-tier concept, hemodynamic relevance of the fixed components is featured by the slitlike ostium and proximal narrowing, while the dynamic component is represented by the acute take-off angle, elliptic vessel shape, and, most importantly, the intramural course. Elements of the fixed component correspond best to the concept of obstructive coronary stenosis known from CAD, that is, flow restrictions based on the static reduction of the cross-sectional area. Accordingly, assessment can be performed similarly to patients with CAD, including determination of percentage of cross-sectional area stenosis of the anomalous in relation to the unobstructed, distal reference segment,37 or measurement of the pressure gradient over the anomalous segment, that is, fractional flow reserve (FFR) or noninvasive ischemia testing using adenosine as a pharmacologic vasodilator.38 Revascularization may then be
considered in case of a reduction of the cross-sectional area >50% in the intravascular ultrasound (IVUS) or an FFR <0.80 or the presence of noninvasive assessed ischemia. Of note, FFR cutoff values are adopted from the experience in CAD and have not been validated in ACAOS. Conversely, anatomic features of the dynamic component (which may represent the main driver for ischemia in ACAOS) gain hemodynamic relevance only during exercise and elevation of stroke volume, blood pressure, and heart rate. Of note, pharmacologic vasodilatation cannot assess the dynamic components, as it requires an increased cardiac output with subsequent augmented vessel wall stress of the aorta. These exercise-induced adaptations can provoke a lateral compression sufficient to cause myocardial ischemia (even during diastole). Therefore, physical stress or positive inotrope/positive chronotrope protocols including volume infusion to mimic strenuous exercise are needed to depict ischemia by dynamic compressions. Angelini et al illustrated this concept in a study using IVUS under rest and during dobutamine infusion, a beta-sympathomimetic drug that increases heart rate and stroke volume. Furthermore, not only the presence but also the extent of the intramural course seems to be relevant. In particular, the peculiar anatomic characteristic of the length related to the width of the intramural segment itself may mostly contribute to the dynamic component and therefore to the pathophysiology of ACAOS. The normal anatomic origin and intraparietal aortic wall course of a coronary artery is characterized by an exit angle, which is approximately equal to 90° (Figure 1A). On the contrary, when there is an abnormal angulated orifice, the coronary vessel passes obliquely through the aortic wall for a distance (a), which is equal or inferior to the coronary artery’s diameter (b), and the exit-angle ranges typically between 45° and 90° (Figure 1B). Finally, in the presence of an abnormal intramural course, the coronary vessel passes obliquely through the aortic wall for a distance (a), which is greater than the coronary artery’s diameter (b), and the exit-angle is about >0° to 45° (Figure 1C). In this latter case, the length of the intramural tract is greater than the coronary diameter (a>b). The latter diagram clarifies that the longer the intramural tract is, the more prone it is to intraparietal compression during acute systolic blood pressure increase, as in strenuous physical effort, which can justify the increased ischemic risk for this anatomic characteristic. Intuitively, the longer the tract is, the higher the risk of prolonged coronary occlusion, but there are currently no data supporting this hypothesis, which could also help predict and stratify the ischemic risk. Several studies have shown that the length of the intramural segment as well as the extent of the elliptic proximal vessel shape (defined as height/width ratio of >1.3) is associated with an increased risk for ischemia. However, in previous studies, none of the anatomic features correlated independently with ischemia. Thus, a complex interplay between the different dynamic and fixed components has been suggested. In addition, hemodynamic relevance depends on the supplied myocardial mass as well as other contributing factors (eg, volume status and type of physical activity). Further, several findings suggest an age

Figure 1. Illustration with variants of proximal coronary artery anatomy.
A. The normal anatomic origin and intraparietal aortic wall course of a coronary artery, and the exit angle is equal to ≈90°. B. The abnormal angulated orifice: the coronary vessel passes obliquely through the aortic wall for a distance (a) that is equal or inferior to the coronary artery’s diameter (b), and the exit-angle is <90°. C. The abnormal intramural course: the coronary vessel passes obliquely through the aortic wall for a distance (a), which is greater than the coronary artery’s diameter (b), and the exit-angle is about >0° to 45°. Of note, proximal narrowing exceeds the intramural course in most cases. Hence, juxta-aortic calibers are frequently smaller than the distal reference calibers.
The round vessel shape at the distal reference site (B5 left coronary artery with 1 injection (projection: left anterior-oblique 84°, caudal 7°). Invasive physiologic assessment with FFR during a dobutamine-volume challenge demonstrating absence of hemodynamic relevance. A6, Invasive coronary angiography illustrating both the anomalous and atherosclerotic lesions originating from the opposite sinus of Valsalva.

DIAGNOSTIC MANAGEMENT OF ACAOS

Based on the complex pathophysiologic mechanisms of myocardial ischemia in patients with ACAOS, the clinical presentation is heterogeneous.14 In fact, most patients are asymptomatic; however, encountered symptoms may include angina pectoris, exercise-related or -unrelated chest pain, palpitations, dyspnea, dizziness, syncope, and myocardial infarction as well as SCD.6,11,28,37,51–64 Besides acute ischemia–induced arrhythmias, repetitive minor ischemic events with consecutive myocardial fibrosis may serve as a substrate for ventricular tachyarrhythmias and SCD.6,65 Consequently, multimodality diagnostic management of patients with ACAOS should not only imply the detection of anatomic high-risk features and myocardial ischemia of ACAOS but also provide information for possible myocardial fibrosis/scar in suspected cases (Figure 2).14,15,30

We recently proposed a testing algorithm in individuals who present with stable symptoms or who are asymptomatic with suspected or confirmed ACAOS. The testing algorithm includes anatomic and ischemia testing with the main goal to differentiate hemodynamically relevant ACAOS from innocent coincidental bystanders.22 Of note, in patients with ACAOS presenting in an acute setting (ie, myocardial infarction, troponin leakage) direct revascularization should be aimed.65 Based on previous studies showing a reduced risk for potentially serious adverse events with increasing age,13,33,35,66 the diagnostic downstream testing recommendations have been adapted to age (below and above 30 years old). One has to be aware that dichotomization of the age 30 years is arbitrary and should not be seen as a stringent recommendation but should rather be seen as a guidance.

Noninvasive Diagnostic Assessment

In the population <30 years of age, and especially in the pediatric population, the initial diagnostic modality should be transthoracic echocardiography by an experienced sonographer. Transthoracic echocardiography enables the imaging of the origin and the proximal course of the coronary arteries noninvasively and without radiation exposure.46,67 If ACAOS cannot be ruled out with certainty (eg, low acoustic window quality48) or in cases in which ACAOS is confirmed, additional imaging is required to assess and quantify the anatomic high-risk features including the intramural course. Coronary computed tomography angiography (CCTA) or cardiac magnetic resonance (CMR) imaging are ideal anatomic diagnostic modalities in ACAOS, whereas CCTA provides the

Figure 2. Comparison of the diagnostic management in 2 similar cases of R-ACAOS.

A, A 65-year-old woman with atypical chest pain and exertional dyspnea (New York Heart Association class II) since 4 months. Normal electrocardiographic and echocardiographic (LVEF 60%) findings, bicycle exercise testing with exercise-induced dyspnea without ischemic ECG alterations at heart rate (HR) 154/min (99% of maximum HR), A1 and A2, Coronary computed tomography angiography showing absence of coronary artery diseases (CAD), a R-ACAOS with acute take-off angle (18.3°), an intramural course (7.8 mm) and an elliptic vessel shape (ratio 2.8). No slitlike ostium or proximal narrowing could be illustrated. A3, Single-photon emission computed tomography with physical stress showing no exercise-induced myocardial ischemia at a HR of 155/min. A4, Invasive coronary angiography illustrating both the anomalous and the left coronary artery with one injection (projection: right anterior-oblique 2°, caudal 8°). A5, Invasive physiologic assessment with FFR during a dobutamine-volume challenge demonstrating absence of hemodynamic relevance. B, A 48-year-old man with fatigue, atypical chest pain, and occasionally dyspnea/palpitations since 6 months. Normal electrocardiographic and echocardiographic (LVEF 60%) findings, bicycle exercise testing without symptoms or ischemic ECG alterations at max. HR of 167/min (97% of maximum HR), B1 through B3, CCTA showing absence of CAD, an R-ACAOS with acute take-off angle (3.9°), an intramural course (14.3 mm), an elliptic vessel shape (ratio 3.4) as well as a slitlike ostium. No relevant proximal narrowing could be illustrated. B4 and B5, Illustration of the oval vessel shape within the intramural course (B4) and normalization of the round vessel shape at the distal reference site (B5). B6, Invasive coronary angiography illustrating both the anomalous and the left coronary artery with 1 injection (projection: left anterior-oblique 84°; caudal 7°) Invasive physiologic assessment with FFR(dobutamine) demonstrating hemodynamic relevance of the anomalous course. CAD indicates coronary disease; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; and R-ACAOS, right anomalous coronary artery originating from the opposite sinus of Valsalva.
best noninvasive spatial resolution as well as the possibility to evaluate the full course of the coronary arteries. One of the main advantages of CMR is that it inherits the ability to visualize and assess the origin and the proximal course of the anomalous coronary artery without radiation. Whether CMR may further help to detect patchy myocardial necrosis with regard to SCD prevention in ACAOS is under discussion. In cases of
ACAOS without anatomic high-risk features (“benign” variants), no further testing is needed. In all other cases, noninvasive and if applicable invasive functional testing is recommended (ie, transthoracic echocardiography, CMR, single photon emission computed tomography or positron emission tomography using physical exercise or dobutamine stimulation).

In the population >30 years of age, direct CCTA is recommend to assess the presence or absence of concomitant CAD.

**Invasive Diagnostic Assessment**

For decades, invasive coronary angiography has been seen as the anatomic diagnostic gold standard in patients with ACAOS. However, currently state-of-the-art CCTA/CMR is preferred because of its lower costs and the ability to noninvasively provide high-resolution visualization of the anatomic high-risk features, whereas invasive coronary angiography serves rather as an alternative modality in defining the anatomy of ACAOS. However, invasive coronary angiography in combination with intravascular imaging such as IVUS or optical coherence tomography still plays an important role in assessing high-risk features. Although optical coherence tomography provides a better spatial resolution, it is limited by a larger probe diameter and requires continuous contrast agent injection during recording. Two limitations especially relevant in ACAOS with a slitlike ostium and high-grade proximal narrowing. Further, IVUS and invasive FFR are the preferred modality to assess functional, dynamic changes under stress conditions.

**Stress Protocols in ACAOS**

One must be aware that noninvasive functional testing in ACAOS might lead to false-negative results, especially after submaximal stress protocols. When choosing a noninvasive functional testing, myocardial perfusion stress positron emission tomography might represent the most sensitive technique, as it allows not only a qualitative but also a quantitative assessment of the coronary flow under stress and resting conditions. However, probably the most adequate hemodynamic assessment of ACAOS includes an invasive physiologic evaluation under a dobutamine/volume challenge (ie, IVUS/optical coherence tomography and FFR). The protocol aims to reach, if possible, a maximal stress test (ie, 100% of the maximal heart rate, estimated by the formula 220 minus age) by using a dobutamine dose up to 40 μg/kg per body weight per minute as well as steady infusion of saline during the whole procedure (usually >1500 mL to prevent a preload decrease). If target heart rate cannot be achieved, 1 mg of atropine can be added to the ongoing dobutamine infusion. It is important to note that the intubation of the anomalous ostium in combination with advanced diagnostic including FFR and intravascular imaging requires a high level of expertise and should be performed by ACAOS-experienced interventional cardiologists. Potential but rare risks include aortic or coronary dissections with consecutive myocardial infarction or stroke. Further, the invasive assessment using a dobutamine challenge is not feasible in every patient and especially poses difficulties in the pediatric population, where invasive imaging frequently requires general anesthesia. In these cases, noninvasive functional imaging might be the preferred approach. Consequently, it is recommended to refer patients with ACAOS to a specialized and experienced tertiary center where coronary artery anomalies are interdisciplinarily managed by cardiac imaging specialists, interventional cardiologists, and heart surgeons.

**THERAPY OF PATIENTS WITH ACAOS**

Because of the complex pathological mechanisms of myocardial ischemia in patients with ACAOS, a uniform treatment strategy is not applicable. Based on the presence of different anatomic high-risk features, possible concomitant CAD, and functional imaging, an individually tailored therapy is advised (see Table 1). Of note, the pre- and postoperative diagnostic assessment in published trials is heterogeneous, and evidence of ACAOS-related myocardial ischemia exists only in few studies. Because of the limited information on the diagnostic workup, evidence is lacking whether the indication for surgical correction of ACAOS was truly beneficial or whether the operation was performed in hemodynamic nonrelevant anomalies. Consequently, thorough verification of the therapeutic success is not possible on the basis of the existing published data.

**Surgical Management**

Surgical revascularization is the primary treatment strategy in patients with hemodynamically relevant ACAOS. An overview of the most relevant clinical trials with regard to treatment of patients with ACAOS is depicted in Table 2. Although coronary “unroofing” is the most common surgical procedure reported in the literature, currently there are no recognized guideline recommendations on surgical techniques (neither in the American Heart Association/American College of Cardiology 2018 guidelines nor in the European Society of Cardiology 2020 guidelines). Various surgical techniques have been reported, and the most common procedures with their advantages and limitations are outlined below.

**Coronary Unroofing/Neo-Ostium Creation**

In ACAOS with the presence of an intramural course, coronary unroofing is the preferred surgical revascularization therapy according to a recent study by the
Table 1. Overview of the Therapeutic Possibilities

| Anatomic high-risk features to be addressed | Coronary unroofing/Neo-ostium | Translocation/Reimplantation | Coronary ostioplasty | CABG | Pulmonary artery translocation | PCI | Conservative management |
|--------------------------------------------|-------------------------------|-------------------------------|----------------------|------|-------------------------------|-----|---------------------------|
| Fixed components                           |                               |                               |                      |      |                               |     |                           |
| Sitllike ostium                            | ++                            | +                             | +++                  | ++   | −                             | +   | −                         |
| Proximal narrowing                         | ++                            | ++                            | +++                  | ++   | −                             | +   | −                         |
| Dynamic components                         |                               |                               |                      |      |                               |     |                           |
| Acute take-off angle                       | ++                            | +++                           | ++                   | ++   | −                             | −   | −                         |
| Intramural course with lateral compression | +++                           | +++                           | +++                  | ++   | −                             | +   | +                         |
| Advantages                                 |                               |                               |                      |      |                               |     |                           |
| Largest clinical evidence                  |                               | Applicable in different anatomic situations | True anatomic repair | Large technical experience from CAD | Low procedural risk | Low-invasive | No surgery/good option in low-risk or asymptomatic middle-aged/older population |
| Limitations                                |                               |                               |                      |      |                               |     |                           |
| Risk of aortic regurgitation and remaining stenosis, length of the intramural course | Challenging procedure requiring coronary mobilization; circumferential anastomosis | Challenging procedure, unclear long-term outcome of patch plastic | Competitive flow through anomalous native segment causing graft failure | Does not address important anatomical high-risk features | Unclear long-term stent patency/possible restenosis and outcome | Negative emotional and health aspects |

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; and PCI, percutaneous coronary intervention; conservative management=medical therapy (eg, beta-blocker) and sports restrictions.
Table 2. Overview of the Most Relevant Clinical Trials With Regard to Treatment of Patients With ACAOS

| Authors                     | Journal                          | Year of publication | Population | Symptoms                  | Diagnostic assessment                                      | Therapeutic management          | Outcome                               | Limitations                                                                 |
|-----------------------------|----------------------------------|---------------------|------------|---------------------------|-----------------------------------------------------------|---------------------------------|---------------------------------------|--------------------------------------------------------------------------------|
| Jegatheeswaran et al 152     | J Thorac Cardiovasc Surg.        | 2020               | n=682; median age, 12.9 y | R-ACAOS 74% L-ACAOS 24% | Not reported                                           | Preoperative ischemia testing 41%, 64/395 positive Cardiac imaging unclear | Surgery 24%                           | 3% coronary-related reoperations 1% death at 30 d                          |
|                             |                                  |                     |            |                           |                                                           |                                 | Median FU, 2.8 y                | Postoperative ischemia testing 48%, 26/395 positive                        |
| Mery et al 153              | J Thorac Cardiovasc Surg.        | 2018               | n=162; median age, 14 y | R-ACAOS 72% L-ACAOS 15%  | Data only available for surgical patients None 27% Typical AP 36% Atypical AP 36% Dyspnea 7% Palpitations 9% Syncope 21% SCA 7% | Echocardiography CCTA Stress nuclear perfusion imaging | Surgery 38%                           | 3-month FU, 96% 17% abnormal nuclear perfusion imaging, 12% with mild ostial stenosis in the CCTA |
|                             |                                  |                     |            |                           |                                                           |                                 | Median FU, 2 y                | Osteopathy 2% 4. Side-side-anastomosis 2% Conservative 62%                  |
|                             |                                  |                     |            |                           |                                                           |                                 | Postoperative ischemia testing 54%, 26/395 positive | Short follow-up, broad indication for surgery (L-ACAOS, symptoms suggestive of ischemia, positive functional test, high-risk anatomy) |
| Padalino et al 154          | Eur J Cardiothorac Surg.         | 2019               | n=156; median age, 39.5 y | R-ACAOS 68% L-ACAOS 22% | None 13% Typical AP 27% Dyspnea 6% Palpitations 5% Syncope 9% SCA 14% | Echocardiography 96% CCTA 72% Functional testing occasionally | Unroofing 56% Reimplantation 19% CABG 15% (older patients)                |
|                             |                                  |                     |            |                           |                                                           |                                 | Osteopathy 6% PA translocation 1% | Operative mortality 1.3%, 9% with major postoperative complications Median FU, 2 y 5 coronary-related AE, 14% with persistent symptoms (undefined chest pain) |
|                             |                                  |                     |            |                           |                                                           |                                 | Median FU, 2 y                | No exact anatomic description, few functional assessment                  |
| Fabozzo et al 155           | Semin Thorac Cardiovasc Surg.    | 2016               | n=155; median age, 8.5 y | R-ACAOS 82% L-ACAOS 18%  | None 48% Typical AP 14% Atypical AP 10% Syncope 10% SCA 3% Myocardial infarction 1% | Echocardiography 90% CAG 20% CMR or CT 57% Stress echocardiography 22% SPECT 19% | Surgery 46%                           | Major perioperative complications 4% Median FU, 1.9 y Stress-testing 53% no evidence of ischemia on perfusion imaging |
|                             |                                  |                     |            |                           |                                                           |                                 | Total positive stress test=7% | Low rate of confirmed myocardial ischemia                                |
| Poynter et al 156           | World J Pediatr Congenit Heart Surg. | 2014               | n=113; median age, 12.6 y | R-ACAOS 69% L-ACAOS 29%  | Not reported                                           | Not reported                    | Unroofing 88% Reimplantation 10% PA translocation 6% Osteoplasty 3% CABG 2% | Not reported                                                                 |
|                             |                                  |                     |            |                           |                                                           |                                 |                         | No information on diagnostic assessment and outcome                        |
| Authors          | Journal                        | Year of publication | Population | Symptoms | Diagnostic assessment | Therapeutic management | Outcome               | Limitations                                     |
|------------------|--------------------------------|---------------------|------------|----------|-----------------------|------------------------|-----------------------|------------------------------------------------|
| Courand et al    | Int J Cardiol.                 | 2021                | n=100, mean age 24±19 y | None 25% | Echocardiography 65%  | Surgery 61% 1. Reimplantation 98% 2. Unroofing 2% Medical therapy 39% | Mean FU, 4.9±5.3 y No death for any of the groups, no recurrence of symptoms for the operated patients | No exact anatomic description, few functional assessment |
| Mainwaring et al | Eur J Cardiothorac Surg.       | 2014                | n=76; median age, 15 y | None 21% | Echocardiography OCTA | Unroofing 72% Reimplantation 9% PA translocation 18% | No operative mortality, no reoperation Mean FU, 6 y No new evidence for myocardial ischemia | No functional assessment |
| Sharma et al     | Ann Thorac Surg.               | 2014                | n=75; mean age, 40±20 y | None 28% | OCTA GCA Stress test 53%, 20/40 positive | Unroofing 100% 3% additional CABG on the anomalous vessel Mean FU, 1.56±0.2 y, no reported symptoms, negative stress and anatomic FU test | Low rate of confirmed myocardial ischemia |
| Angelini et al   | Catheter Cardiovasc Interv.    | 2015                | n=67; mean age, 46±12 y | None 12% | OCTA (36%) CAG with IVUS and dobutamine-volume challenge (100%) | PCI (62%) Surgical (4%) Medical (33%) | Mean FU, 5.0±2.9 y 2/23 positive nuclear study; 4/10 CAG with in-stent restenosis | Low rate of repeated invasive assessment |
| Sachdeva et al   | J Thorac Cardiovasc Surg.      | 2017                | n=63; median age, 13 y | None 46% | Echocardiography 95%  | Unroofing 100% | No surgical mortality, no coronary reinterventions Median FU, 3.1 y Stress testing without evidence for reversible ischemia; 3 sudden SCA (1/3 death) | Low rate of confirmed myocardial ischemia No exact anatomic description |

Table 2. Continued
| Authors       | Journal                  | Year of publication | Population          | Symptoms                                      | Diagnostic assessment                                      | Therapeutic management                                      | Outcome                      | Limitations                                                                 |
|--------------|--------------------------|---------------------|---------------------|-----------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------|
| Kaku et al   | Jpn Circ J.              | 1996                | n=56; mean age, 56±12| R-ACAOS 79% L-ACAOS 0%                        | None 13% Typical AP 40% Atypical AP 38% Dyspnea 2% Palpitations 4% Syncope 2% | GAG with ergovine (2/7 positive) Stress ECG (16/33 positive) SPECT (4/9%) | Exercise restriction (4/44) Medical treatment (13/44) Both (12/44) None (15/44) | Mean FU, 5.6±4.2 y (n=44) No deaths attributed to the anomaly Low rate of confirmed myocardial ischemia No imaging of the anatomic high-risk features |
| Kara et al   | Eur J Cardiothorac Surg.  | 2021                | n=39; median age, 14 y| R-ACAOS 72% L-ACAOS 28%                       | None 20% Chest pain 56% Dizziness 33% Dyspnea 15% Syncope 13% Cardiac arrest 5% (>1 possible) | Stress-test (unspecified) 4/32 positive | Coronary unroofing 77% (33% with additional PA translocation) PA translocation 8% CABG 7% Reimplantation 5% | Median FU, 4 y FU CCTA after 3–6 mo, 3 revascularization procedures Low rate of confirmed myocardial ischemia |
| Davies et al | Ann Thorac Surg.         | 2009                | n=36; mean age, 44±16 y| R-ACAOS 58% L-ACAOS 36%                        | None 29% Chest pain 56% Dyspnea 19% Syncope 6%           | Stress test (unspecified) 9/21 positive | Coronary unroofing 61% CABG 39% | Mean FU, 1.1±2.8 y; 1 patient with recurrent symptoms (CABG; patency flow) No exact anatomic description, few functional assessment |
| Feins et al  | Ann Thorac Surg.         | 2016                | n=31; mean age, 43±3y  | R-ACAOS 77% L-ACAOS 19%                       | None 6% Chest pain 38% Typical AP 27% Dyspnea 19% Palpitations 6% Syncope 6% SCA 6% Myocardial infarction 6% | Not reported | Unroofing 68% Translocation 19% CABG 13% | Mean FU, 3.8±0.8 y 42% FU CCTA, 1/3 mild stenosis 55% functional testing, 2/17 positive (1× CABG, 1× unroofing) No information on preoperative diagnostic assessment |
| Mumtaz et al | Ann Thorac Surg.         | 2011                | n=22; median age, 15 y| R-ACAOS 68% L-ACAOS 32%                       | None 5% Typical AP 68% Syncope 23% Myocardial infarction 5% | Echocardiography (100%) CCTA (77%) CMR 5% Nuclear study 27%, half positive | Coronary unroofing                        | Mean FU, 1.4 y; 5% still symptomatic without evidence of ischemia No exact anatomic description, few functional assessment |
| Ibraheem et al| J Card Surg.              | 2019                | n=16; mean age, 35±5y  | R-ACAOS 100%                                | Typical AP 31% Atypical AP 69% Syncope 38% Palpitations 50% (>1 possible) | CAG CCTA Dobutamine stress echocardiography 7/16 positive SPECT 4/16 positive | CABG 100% including ligation of the RCA in 94% | One in-hospital death 5–FU FLU, 13/16 patent grafts (CCTA) Low rate of confirmed myocardial ischemia |

AE indicates adverse event; ACAOS, anomalous coronary arteries originating from the opposite sinus of Valsalva; AP, angina pectoris; CAG, coronary angiography; CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; FU, follow-up; IVUS, intravascular ultrasound; L-ACAOS, left anomalous coronary arteries originating from the opposite sinus of Valsalva; ns, statistically nonsignificant; PA, pulmonary artery; R-ACAOS, right anomalous coronary arteries originating from the opposite sinus of Valsalva; SCA, sudden cardiac arrest; and SPECT, single-photon emission computed tomography.
Congenital Heart Surgeons Society. After exploration and confirmation of the intramural course using a coronary probe, the common wall with the aorta is sharply excised or incised over the probe along its entire intramural course proximal to the site where it emerges from the aortic wall. In addition, tacking sutures are placed to ensure intimal continuity and prevent dissection. Further, the combination with an “unflooring” technique by augmenting the antiaortic side of the coronary artery with a longitudinal patch has been described. A neo-ostium is formed in the “correct” sinus of Valsalva, usually with an enlargement of the ostium (Figure 3A), and hence, the unroofing procedure includes a component of coronary ostioplasty. The therapeutic procedure of coronary unroofing directly addresses the anatomic high-risk feature slitlike ostium as well as the intramural course with its elliptic vessel shape. However, acute take-off angle is often not completely corrected, and proximal narrowing frequently exceeds the intramural segment. Thus, caliber of the anomalous vessel returns to its normal, distal reference parameter several millimeters distal to the aortic wall. Therefore, a remaining coronary stenosis between the unroofed segment and the distal coronary artery is possible.

Based on the largest body of evidence for a surgical procedure in ACAOS, coronary unroofing should be applied in situations with a long course (ie, up to the appropriate cusp) without contact with the commissure. However, other important anatomic features may limit its ubiquitous application. Especially in cases where the anomalous vessel traverses below or next to the commissure, an unroofing along the entire intramural course could impair the suspension of the aortic valve. In these anatomic variants, the treatment should be characterized by either detaching the commissure or performing a commissural resuspension or aortocoronary window, that is, unroofing before and after the commissure while leaving the commissure intact. In fact, there is evidence that commissural manipulation (defined as takedown or resuspension of the commissure) is associated with a higher risk of postoperative aortic regurgitation. Formation of a neo-ostium at the location where the anomalous vessel emerges from the aortic wall without concomitant unroofing has been described as a valuable alternative.

Further, success of the unroofing procedure depends on the length of the intramural course. Mery et al demonstrated that patients with a long intramural segment benefit the most, whereas a short intramural segment limits the success of the unroofing technique. This is particularly true in cases where the anomalous vessel remains within the incorrect sinus and courses through a thickened commissure or pillar (ie, the aortic wall segment above the commissure). Although in such variants, unroofing may increase the size of the ostium, it does not address compression of the pillar or proximal narrowing. Hence, significant flow restriction may persist as described in the study by Mery et al, where this was the case in 4 of 5 cases as documented in postoperative CCTA. Furthermore, a short intramural course is often associated with an insufficient correction of the acute take-off angle after unroofing and thus persistent hampered coronary flow patterns.

**Coronary Translocation/Reimplantation**

Coronary translocation or reimplantation of the anomalous coronary artery in the appropriate sinus of Valsalva is a method often described in patients with either a short or absent intramural course, where the unroofing technique is limited. Further, re-implantation has been applied in the situation of rare ACAOS variants with intraseptal or intraconal course in combination with a supra-arterial myotomy of the aberrant segment. Coronary translocation starts with careful mobilization of the proximal coronary artery in the epicardial fat, followed by a transection with aortic button and reimplantation in the “correct” sinus of Valsalva using an aortic punch or a medial trap-door technique. Afterwards, the ostium’s original location is closed with a small prosthetic patch (Figure 3B). Alternatively, translocation of the anomalous coronary artery by transecting it just as it emerges from the aortic wall has been described. The proximal stub is then oversewn and the coronary artery reimplanted by an end-to-site anastomosis. Similar to coronary unroofing, coronary translocation corrects the anomalous intramural course. However, a slitlike ostium and proximal narrowing are often not corrected, requiring an additional procedure, that is, coronary ostioplasty. In general, coronary translocation is a challenging procedure and involves extensive dissection and manipulation of the artery, both associated with complication as neo-ostial obstruction, kinking, and flow disruption. In addition, the long-term effect of a circumferential anastomosis, especially in young patients, is unknown.

**Coronary Ostioplasty**

Coronary ostioplasty (ie, “anatomic surgical repair”) refers to a surgical technique with complete reconstruction of the anomalous coronary ostium. This procedure (Figure 3C) starts with transection of the aortic wall followed by an incision from the cut edge of the aorta into the ostium of the anomalous coronary artery and extended into the anomalous vessel. Finally, a triangular patch (usually pericardium) is sutured into this incision, resulting in the creation of a neo-ostium as well as an enlarged proximal segment. By creating...
a new and wider coronary ostium in the appropriate sinus and additional enlarging of the proximal vessel course, coronary angioplasty directly addresses all anatomic high-risk features.\textsuperscript{96,98} However, similar to coronary translocation, coronary ostioplasty is a technically challenging procedure, where a high expertise is required, and long-term follow-up data on the application of a patch in the coronary circulation are missing. Concerns about thrombus formation in addition to aneurysmal alterations of the patch have been rarely reported.\textsuperscript{96,99}

**Coronary Artery Bypass Graft Surgery**

Standard coronary artery bypass grafting (CABG) is a well-established surgical procedure for treatment of CAD and is preferred in certain circumstances of patients with ACAOS. Compared with unroofing or coronary translocation/ostioplasty, no manipulations at the aorta or near the aortic valve are needed in CABG, thus reducing procedural risks.\textsuperscript{64} Although from the pathophysiologic point of view CABG addresses all anatomic high-risk features, as it directly eliminates the anomalous segment, several important limitations have to be considered to this approach. First and most important, there is an increased risk of coronary bypass failure based on the competitive flow through the native anomalous segment.\textsuperscript{64,76,100–103} In fact, a high graft failure rate has been described in the literature,\textsuperscript{103–107} and therefore proximal ligation of the anomalous coronary artery has been described as a crucial step for CABG patency.\textsuperscript{64,76,85,105,108} An important drawback of this procedure is the complete dependence of the anomalous supplied myocardium on a graft and anastomosis with uncertain durability and, especially important in young patients, uncertain growth potential.\textsuperscript{84,103} Hence, several studies propose that CABG should be limited to only those patients with concomitant, significant CAD within the anomalous vessel.\textsuperscript{85,104,108}
Pulmonary Artery Translocation

The pulmonary artery translocation approach is characterized by dividing the main pulmonary artery at its bifurcation and shifting leftward, while a patch suture enlarges the pulmonary artery confluence (Figure 3D). Alternatively, pulmonary artery translocation can be performed by moving the pulmonary arteries anterior to the aorta (modified LeCompte maneuver). Both procedures result in the creation of additional space between the great arteries, addressing the historically believed compression of the anomalous segment between the great arteries. However, this mechanism is unlikely considering the pressure condition in the respective circulatory systems. Further, pulmonary artery translocation does not address any of the other anatomic high-risk features. Indeed, most of the reported (successful) applications of this technique were in combination with unroofing or in patients with the interarterial course as the only risk factor (ie, with unclear hemodynamic significance of the ACAOS). Hence, from the pathophysiologic point of view, there is no indication for this procedure in patients with ACAOS.

Percutaneous Coronary Intervention

There is limited evidence for the use of percutaneous coronary intervention (PCI) in the setting of ACAOS. In most case reports, PCI targets atherosclerotic lesions distal to the anomalous segment, and thus it does not represent a corrective treatment of ACAOS itself. There is 1 clinical trial describing PCI in 42 middle-aged and older patients with R-ACAOS, where stenting was conducted under intravascular ultrasound guidance. The authors aimed at covering the entire intramural segment with a single stent matched with the distal reference diameter. They successfully increased the cross-sectional area of the intramural segment from 4.8 mm² to 10.8 mm² (mean distal reference cross-sectional area=12.4 mm²) when applying this approach. Further, lateral compression as well as phasic pulsatility were eliminated after stent deployment. PCI address mainly the slitlike ostium, the proximal narrowing, and the lateral compression of the intramural segment, while the acute take-off angle is not touched (Figure 4). Of note, there is no evidence of the behavior of a stent exposed to prolonged and repeated external dynamic compression in such circumstances, and more importantly, there is currently no indication for this procedure in a pediatric and young patient population considering the coronary growth and unknown long-term results. However, whether this approach might be an alternative in patients less suitable for surgery is unclear, as long-term outcome after stent implantation in the intramural segment remains unclear. In fact, 40% (4/10) of the patients who underwent clinically indicated follow-up coronary angiography demonstrated relevant restenosis requiring revascularization in the above-mentioned study. Therefore, PCI is currently rather an ultimate option in nonsurgical candidates until more evidence is available from future trials on the long-term patency of PCI in ACAOS. However, it is plausible that with this growing evidence, PCI will become a valuable therapeutic option for the treatment of ACAOS, especially in older patients.

Conservative Management

Based on the pathophysiology with exercise-dependent aggravation of the flow restriction (ie, the dynamic component), a conservative management with sports restriction and medical therapy (ie, beta-blocker) is possible but should not be promoted as the first-line therapy. In fact, most institutions recommend these measures only for bridging patients until the surgical intervention is performed or in cases in which affected patients declined an operation or an operation is not feasible. Especially for young patients, long-term exercise restriction or beta-blocker therapy can represent a radical limitation with subsequent negative emotional and health aspects. Hence, conservative management is not an option for athletes or young, active individuals. Accurate diagnostic assessment is crucial, as patients with variants and absence of hemodynamic relevance should not be limited in their sports behavior. Finally, reports of sudden cardiac arrest have been reported even after surgical therapy of the anomaly. As a reason for this, an incomplete revascularization or a possible underlying arrhythmogenic substrate in ACAOS with previous myocardial damage have to be considered. Therefore, the addition of antiarrhythmic medication (eg, beta-blocker) might be considered in such circumstances.

PROPOSED THERAPEUTIC MANAGEMENT ALGORITHM

Based on the pathophysiology of ACAOS, we propose the following therapeutic management algorithm aiming at correcting the different anatomic high-risk features and restoring hemodynamic physiology. The certainty whether ACAOS with anatomic high-risk features (ie, including 1 or multiple features: interarterial course, intramural course, acute take-off angle, slitlike ostium, proximal narrowing, proximal elliptic vessel shape) is a coincidental or a hemodynamically relevant finding is the first and most prominent step in the decision making toward the appropriate therapeutic management. ACAOS-related myocardial ischemia by FFR ≤0.80 or minimal lumen area reduction of >50% in IVUS using a dobutamine/volume challenge or presence of ischemia...
in noninvasive imaging is an indication for correction of the anomalous vessel.\textsuperscript{30,49} If the patient is asymptomatic and does not show any ACAOS-related ischemia, no further actions are advised. However, in symptomatic patients with nonhemodynamically relevant ACAOS, other underlying causes of the symptoms (eg, nonanomalous CAD) should be investigated before a case-by-case decision is made toward ACAOS correction or not. In all cases with hemodynamically relevant ACAOS, the subsequent step involves the assessment of presence or absence of concomitant CAD. If needed and in unclear cases, fused/hybrid cardiac imaging can help in the distinction of anomalous versus nonanomalous vessel-related ischemia.\textsuperscript{30,49} In addition, sports restrictions (particularly competitive sports) are recommended during this diagnostic and therapeutic process. Based on the information from noninvasive and invasive imaging on the presence and extent of anatomic high-risk features,\textsuperscript{22} the optimal surgical therapy is selected.\textsuperscript{8,22,125}

**Presence of an Intramural Course**

In the situation of a long intramural course from the wrong sinus up to the appropriate sinus of Valsalva, above the commissure, unroofing is the recommended approach. In cases with a short intramural course limited within the wrong sinus of Valsalva, or in cases with a long intramural course but a course below the commissure, the formation of a neo-ostium or a coronary translocation would be an alternative strategy to unroofing. Of note, decision for creation of a neo-ostium or coronary translocation depends on the attainable angle of the neo–take-off. Further, in situations in which relevant proximal narrowing exceeds the intramural course, an additional patch angioplasty should be considered.

**Absence of an Intramural Course**

Absence of an intramural course requires alternative treatment strategies, as the surgical technique with the best level of evidence, that is, coronary unroofing, is not applicable. In the combination of the absence of the intramural course and absence of a slitlike ostium and proximal narrowing, coronary translocation and considering additional patch angioplasty of the anomalous coronary artery is the recommended surgical procedure. In the situation of the presence of a slitlike ostium or proximal narrowing (ie, both features representing a fixed component and thus causing flow
restrictions similar to a fixed stenosis known from atherosclerotic lesions), coronary translocation with or without patch ostioplasty should be the best choice for children and adolescents, while CABG should be considered in older patients, as competitive flow will not limit graft patency. Alternatively, in the situation of a proximal narrowing as the only culprit feature, PCI may be considered in the older population with high operative risk as a valuable ultima ratio alternative.

**Presence of Concomitant CAD**

With increasing age, concomitant CAD gains importance and impacts on the therapeutic decision. In such situations, fused/hybrid cardiac imaging helps to differentiate between CAD-related from ACAOS-related perfusion deficits. In cases of atherosclerotic lesions within the anomalous vessels and a demonstrated hemodynamic relevance of the ectopic course, CABG is the recommended therapy of choice as the risk of graft failure attributable to low competing flow through the native vessel vanishes. In the case of CAD in nonanomalous coronary arteries, CAD should be addressed as recommended by the guidelines on myocardial revascularization (CABG or PCI), whereas ACAOS should be treated according to anatomic features.

**Eligibility for Sports**

Based on the evidence from autopsy studies, where ACAOS is one of the leading causes of sports-related SCD, strenuous exercise should be avoided in suspected cases of hemodynamically relevant ACAOS until completion of a workup. However, considering the required supramaximal testing to demonstrated

---

**Figure 5.** Flow chart of the therapeutic management in patients with an anomalous coronary artery and confirmed myocardial ischemia related to ACAOS. ACAOS indicates anomalous coronary artery originating from the opposite sinus of Valsalva; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.
hemodynamic relevance, low-intensity sports (eg, golf, yoga) are allowed in all cases if asymptomatic. After surgical correction and exclusion of proarrhythmogenic substrates, reuptake of competitive sports is safe after an appropriate recovery period (eg, 3 months).

GAPS OF KNOWLEDGE

As most of the evidence of therapeutic management in ACAOS is based on small studies/registries, case series, or case reports, the following gaps of knowledge and future research questions aiming at improving evidence-based treatment of ACAOS are highlighted below. Ongoing large single-center and multicenter registries, currently actively recruiting patients, will ideally provide clarifying data for the improvement of the decision making in this clinical setting.

1. In which situations is a surgical intervention required in patients with ACAOS, and what are the most important clinical and imaging findings for the indication of a surgical correction?
2. What is the long-term outcome of the different surgical approaches? Does the anatomic correction versus conservative treatment result only in symptom relief, or can cardiac death be improved as well?
3. What is the optimal method to assess and evaluate the anatomic high-risk features? A universal definition including standardized assessments and thresholds is required.
4. Which patients may be candidates for conservative medical treatment?
5. In which patients does PCI represent a possible minimally invasive treatment option?
6. Should patients with myocardial damage attributable to ACAOS (ie, scarring as an underlying possible arrhythmogenic substrate) be treated surgically and with antiarrhythmic drugs or even with an implantable cardioverter defibrillator?
7. How should patients with surgically corrected ACAOS be followed up?
8. How should we manage asymptomatic patients with hemodynamically relevant ACAOS, and how should we treat symptomatic patients with no hemodynamically relevant ACAOS?
9. Is the application of the adopted FFR threshold of 0.80 as a decision-making tool in ACAOS associated with an improved outcome, as previously demonstrated in the CAD population? What is an optimal cutoff of ischemia burden in nonischemic testing to decide toward ACAOS correction?
10. Coronary dominance determines the location and amount of myocardium perfused by the right or left coronary artery (right or left dominance). The correlation between ACAOS, coronary dominance, and ischemic presentation is still unknown. Further studies are needed to evaluate this potential additional risk factor.
11. What is the best method to assess the success of surgical correction intraoperatively?

CONCLUSIONS

Thorough anatomic and hemodynamic assessment of patients with ACAOS is needed to guide optimal therapeutic management. Because of the heterogeneous presentation of ACAOS, usually an interdisciplinary case-by-case decision is made on the basis of multimodality imaging to tailor the optimal therapeutic management. In patients with ACAOS and a long intramural anomalous vessel course and proven hemodynamic relevance, surgical unroofing is the recommended approach. On the contrary, in cases with ischemia and short or absence of the intramural course, coronary translocation or ostioplasty represent the optimal surgical methods. In patients with concomitant CAD within the anomalous vessel, CABG or PCI may be considered as a therapeutic option. Of note, evidence on the therapeutic management in general is limited, and major efforts have to be made to collect data from multinational ACAOS registries with accurate pre- and postoperative diagnostics to increase evidence-based decision making in this clinical setting.

ARTICLE INFORMATION

Affiliations
Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (M.R.B., L.R., A.A., S.W., C.G.); Centre for Congenital Heart Disease, Department of Cardiovascular Surgery, Inselspital, Bern, Switzerland (A.K., M.S.); and Section of Pediatric and Congenital Cardiac Surgery, Department of Cardio-Thoracic and Vascular Sciences, and Public Health, University of Padova, Medical School, Padova, Italy (M.A.P.).

Sources of Funding
This work was supported by the Swiss National Science Foundation Grant Number 200871, NARCO (Noninvasive Anatomical Assessment for Ruling Out Hemodynamically Relevant Coronary Artery anomalies - A Comparison of Coronary CT to Invasive Coronary Angiography) to Dr Gräni.

Disclosures
Dr Räber received research grants to the institution by Abbott Vascular, Biotronik, Boston Scientific, Medis, Sanofi, and Regeneron; and consultation/speaker fees by Abbott Vascular, Amgen, AstraZeneca, Canon, Occlutech, and Vifor. Dr Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daichi Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed. Dr Windecker serves as an unpaid member of the steering/executive group of trials funded by Abbott Vascular, BMS, Boston Scientific, Biotronik, CardioValve, Edwards Lifesciences, MedAlliance, Medtronic, Polares, Sinomed, V-Wave, and Xeltis, but has not received personal payments by any pharmaceutical company or device manufacturer. He is also member of the steering/executive committee group of several investigated-initiated trials that receive funding by industry...
Anomalous origin of the coronary artery arising from the opposite sinus: prevalence and outcomes in patients undergoing CTA. Eur Heart J Cardiovasc Imaging. 2017;18:224–235. doi: 10.1093/ehjci/jev232

33. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20:1640–1647. doi: 10.1016/0735-1097(92)90519-9

34. Chetlin MD, De Castro CM, McAllister HA. Sudden death as a complication of anomalous left coronary artery from the anterior sinus of Valsalva, A not-so-minor congenital abnormality. Circulation. 1974;50:780–787. doi: 10.1161/01.CIR.50.4.780

35. Taylor AJ, Byers JP, Chetlin MD, Virmani R. Anomalous right or left coronary artery from the contralateral coronary sinus: "high-risk" abnormalities in the initial coronary artery course and heterogeneous clinical outcomes. Am Heart J. 1997;133:428–435. doi: 10.1016/S0002-7812(97)70184-4

36. Diao KY, Zhaq Q, Gao Y, Shi K, Ma M, Xu HY, Guo YK, Yang ZG. Prognostic value of dual-source computed tomography (DSCT) angiography characteristics in anomalous coronary artery from the opposite sinus (ACAOs) patients: a large-scale retrospective study. BMC Cardiovasc Disord. 2020;20:25. doi: 10.1186/s12887-019-12185-3

37. Angeli P, Uribe C, Monge J, Tobis JM, Elayda MA, Willerson JT. Origin of the right coronary artery from the opposite sinus of Valsalva in adults: characterization by intravascular ultrasoundography at baseline and after stent angioplasty. Catheter Cardiovasc Interv. 2015;86:199–208. doi: 10.1002/ccd.26069

38. Tomino PA, De Bruyne B, Pijs NH, Siebert U, Lonser RR, Fijten AP, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213–224. doi: 10.1056/NEJMoA0807611

39. Angeli P, Flamand SD. Newer concepts for imaging anomalous aortic origin of the coronary arteries in adults. Catheter Cardiovasc Interv. 2007;69:942–954. doi: 10.1002/ccd.21149

40. Angeli P, Uribe C. Symptomatic right coronary anomalous with dynamic systolic intramural obliteration and isolated right ventricular ischemia. Catheter Cardiovasc Interv. 2019;93:445–447. doi: 10.1002/ccd.28028

41. Lee SE, Yu CW, Park K, Park KW, Suh JW, Cho YS, Youn TJ, Choi DJ, Jung HJ, et al. Physiological and clinical relevance of anomalous right coronary artery originating from left sinus of Valsalva in adults. Heart. 2016;102:114–119. doi: 10.1136/heartjnl-2015-308488

42. Soler AN, Hillard AA, Gordon BM. Functional assessment of anomalous right coronary artery using fractional flow reserve: an innovative modality to guide patient management. Catheter Cardiovasc Interv. 2017;89:316–320. doi: 10.1002/ccd.26660

43. Tsujita K, Maehara A, Mintz GS, Franklin-Bond T, Mehran R, Stone PH, et al. Intravascular ultrasound and pharmacological stress test to evaluate the anomalous origin of the coronary arteries in adults. J Am Coll Cardiol. 2007;69:942–954. doi: 10.1016/j.jacc.2008.11.016

44. de Oliveira DM, Gomes V, Caramori P. Intravascular ultrasound and pharmacological stress test to evaluate the anomalous origin of the coronary arteries in adults. J Invasive Cardiol. 2012;24:E131–E134.

45. Kaushal S, Backer CL, Popescu AR, Koeberl M, Horner JM, Phillips SD, Schaff HV. Surgical unroofing of anomalous aortic origin of a coronary artery from the contralateral coronary sinus: “high-risk” anomalies in the initial coronary artery course and heterogeneous clinical outcomes. Ann Thorac Surg. 2011;92:986–991; discussion 991-2.

46. DeCampli WM, Fleishman CE, Kirshbom PM, Tchervenkov CI, Karamlou T, Blackstone EH, et al. Survival of repair of anomalous aortic origin of a coronary artery in 113 patients: a Congenital Heart Surgeons’ Society report. J Thorac Cardiovasc Surg. 2019;56:696–703. doi: 10.1016/j.jtcvs.2018.07.080

47. Poynter JA, Bondarenko I, Austin EH, DeCampli WM, Jacques JP, Ziemer G, Kirshbom PM, Tchervenkov CI, Karamlou T, Blackstone EH, et al. Repair of anomalous aortic origin of a coronary artery in 113 patients: a Congenital Heart Surgeons’ Society report. World J Pediatr Congenit Heart Surg. 2014;5:507–514. doi: 10.1177/21501351145104162

48. Courand P-Y, Bozzo A, Ninet J, Boussel L, Bakoul M, Galon-Bertali C, Metton O, Mitchell J, de Montclos TP, Walton C, et al. Diagnosis and treatment of anomalous aortic origin of coronary artery: a twenty-year retrospective study of outcome and decision-making in children and young adults. Int J Cardiol. 2021;337:54–61. doi: 10.1016/j.ijcard.2021.04.066

49. Mainwaring RD, Reddy VM, Reinhardt O, Petrossian E, Punn R, Hanley FL. Surgical repair of anomalous aortic origin of a coronary artery. Eur J Cardiothorac Surg. 2014;46:20–26. doi: 10.1093/ejcts/ezt014

50. Sharma V, Burkhart HM, Dearani JA, Suri RM, Daly RC, Park SJ, Horner JM, Phillips SD, Schaff HV. Surgical unroofing of anomalous aortic origin of a coronary artery: a single-center experience. Ann Thorac Surg. 2014;98:941–945. doi: 10.1016/j.athoracsur.2014.04.114

51. Sachdeva S, Frommelt MA, Mitchell ME, Tweddell JS, Frommelt PC. Surgical unroofing of intracardiac anomalous aortic origin of a coronary artery in pediatric patients: single-center perspective. J Thorac Cardiovasc Surg. 2018;155:1760–1768. doi: 10.1016/j.jtcvs.2017.11.003

52. Cormier C, Hurst J, Zhao Q, Liu H, Hynynen F, Sanders SP, Pigula FA, Del Nido PJ, Nathan M. Anomalous aortic origin of coronary arteries: a single-center experience. Semin Thorac Cardiovasc Surg. 2016;28:791–800. doi: 10.1053/j.semtcv.2016.08.012

53. Mostefa Kara M, Fournier E, Cohen S, Hascoët S, Van Aerschot J, Fuchs TA, Pazhenkottil AP, Gaemperli O, et al. Fused cardiac hybrid magnetic resonance emission tomography in patients with complex coronary artery anomalies. Eur J Radiol. 2016;85:1164–1172. doi: 10.1016/j.ejrad.2015.09.030

54. Hanssen AD, Helsingberg SK, Ahnlund P, Nyberg A, Linde G, Nihlén U, et al. Decision analysis to define the optimal management of athletes with anomalous aortic origin of a coronary artery. J Thorac Cardiovasc Surg. 2018;155:305–319.e4. doi: 10.1016/j.jtcvs.2017.08.116

55.党的十九大报告。
Bigler et al

ACMAGA Management

67. Frommeit PG, Frommeit MA, Tweddell JS, Jaisquiss RD. Prospective echocardiographic diagnosis and surgical repair of anomalous origin of a coronary artery from the opposite sinus with an interarterial course. J Am Coll Cardiol. 2003;42:148–154. doi: 10.1016/S0735-1097(03)00503-8

68. Zeltiser I, Cannon B, Silviana L, Fenrich A, George J, Schleifer J, Garcia M, Barnes A, Riveres S, Patt H, et al. Lessons learned from preparticipation cardiovascular screening in a state funded program. Am J Cardiol. 2012;110:902–908. doi: 10.1016/j.amjcard.2012.05.018

69. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

70. Padalino MA, Jegatheeswaran A, Blitzer D, Ricciardi G, Guariento A. Aortic arch anomalies in adolescents. J Am Coll Cardiol. 2003;50:2078–2082. doi: 10.1016/j.jacc.2007.06.055

71. Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. High-risk cardiovascular conditions in sports-related sudden death: prevalence in 5,169 schoolchildren screened via cardiac magnetic resonance. Tex Heart Inst J. 2018;45:205–213. doi: 10.14503/THU-18-6645

72. Palmieri V, Gervasi S, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Detection of malformations in the coronary arteries. Am J Cardiol. 2019;123:E396–e397.

73. Frommeit PG, Frommeit MA, Tweddell JS, Jaisquiss RD. Prospective echocardiographic diagnosis and surgical repair of anomalous origin of a coronary artery from the opposite sinus with an interarterial course. J Am Coll Cardiol. 2003;42:148–154. doi: 10.1016/S0735-1097(03)00503-8

74. Zeltiser I, Cannon B, Silviana L, Fenrich A, George J, Schleifer J, Garcia M, Barnes A, Riveres S, Patt H, et al. Lessons learned from preparticipation cardiovascular screening in a state funded program. Am J Cardiol. 2012;110:902–908. doi: 10.1016/j.amjcard.2012.05.018

75. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

76. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

77. Vinnakota A, Stewart RD, Najm H, Blackstone EH, Ghobrial J, Stewart RD, Unai S, Pettersson G. Early outcomes of innovative surgical techniques with left thoracotomy for transaortic arch surgery in children. J Thorac Cardiovasc Surg. 2020;169:328–338. doi: 10.1016/j.jtcvs.2020.02.002

78. Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. High-risk cardiovascular conditions in sports-related sudden death: prevalence in 5,169 schoolchildren screened via cardiac magnetic resonance. Tex Heart Inst J. 2018;45:205–213. doi: 10.14503/THU-18-6645

79. Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

80. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

81. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

82. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

83. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

84. Jagers J, Lodge AJ. Surgical therapy for anomalous aortic origin of the coronary arteries. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005;8:122–127. doi: 10.1053/j.pcsu.2005.01.004:122-7

85. Cho SH, Joo HC, Yoo KJ, Youn YN. Anomalous origin of right coronary artery from left coronary sinus: surgical management and clinical result. Thorac Cardiovasc Surg. 2015;63:360–366. doi: 10.1055-s00-0043-157635

86. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro AM, Angelini P, Cheong BY, Lenge De Rosen VV, Lopez JA, Uribe C, Masso AH, Ali SW, Davis BR, Muñucrippi R, Willerson JT. Magnetic resonance imaging-based screening study in a general population of adolescents. J Am Coll Cardiol. 2018;71:579–580. doi: 10.1016/j.jacc.2017.11.051

87. Bigler MR, Seiler C, Räber L, Gräni C, Wolf in sheep’s clothing—The management approach. J Am Heart Assoc. 2021;10:e027098. DOI: 10.1161/JAHA.122.027098.
coronary arteries associated with myocardial ischemia. Am J Cardiol. 2000;86:580–582. a10.
117. Aubry P, Halina du Fretay X, Boudvillain O, Degrel P. Place of angioplasty for coronary artery anomalies with interarterial course. Front Cardiovasc Med. 2020;7:596018. DOI: 10.3389/fcmtd.2020.596018.
118. Hanler JD, Bär S, Ueki Y, Otsuka T, Gräni C, Räber L. Novel diagnostic approach to invasively confirm interarterial course of anomalous right coronary artery. J Am Coll Cardiol Intv. 2020;13:132–134. doi: 10.1016/j.jcin.2019.08.008
119. de Agustín JA, Marcos-Alberca P, Manzano Mdel C, Fernández-Goflin C, Pérez de Isla L, Hernández-Antolín R, Macaya C, Zamorano J. Percutaneous Intervention in a single coronary artery: evaluation of multislice tomography and its feasibility. Rev Esp Cardiol. 2010;63:607–611. doi: 10.1016/j.othj.2010.07.014
120. Unzué L, García E, López-Melgar B, Agudo-Quilez P. Percutaneous treatment of an anomalous left main arising from the opposite sinus with subpulmonic course. Cardiovasc Revasc Med. 2018;19:632–637. doi: 10.1016/j.carrev.2018.01.008
121. Bixby MB. Successful medical management of a patient with an anomalous right coronary artery who declined surgery. Am J Crit Care. 1998;7:393–394. doi: 10.4037/ajcc1998.7.5.393
122. Barbou F, Schiano P, Lahutte M. Anomalous right coronary artery from the left coronary sinus, with an interarterial course. Arch Cardiovasc Dis. 2010;103:626–628. doi: 10.1016/j.acvd.2010.01.010
123. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet (London, England). 2011;378:1244–1253. doi: 10.1016/ S0140-6736(11)60749-6
124. Steptoe A, Butler N. Sports participation and emotional wellbeing in adolescents. Lancet (London, England). 1996;347:1789–1792. doi: 10.1016/S0140-6736(96)91616-5
125. Angelini P, Wainslie R, Cheong BY, Ott DA. Left main coronary artery originating from the proper sinus but with acute angulation and an intramural course, leading to critical stenosis. Tex Heart Inst J. 2010;37:221–225.
126. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2018;40:87–165.
127. Fihn SD, Gardin JM, Abrams J, Berna K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. Circulation. 2012;126:e354–e471. doi: 10.1161/CIR.0b013e31827776a0
128. Brothers JA, Gaynor JW, Jacobs JP, Caldaroni C, Jegatheeswara A, Jacobs ML. The registry of anomalous aortic origin of the coronary artery of the Congenital Heart Surgeons’ Society. Cardiol Young. 2010;20:50–58. doi: 10.1017/S1047951110001095
129. Padalino MA, Franchetti N, Sarris GE, Hazekamp M, Carrel T, Frigola A, Horer J, Roussin R, Oleziou J, Meyns B, et al. Anomalous aortic origin of coronary arteries: Early results on clinical management from an international multicenter study. Int J Cardiol. 2019;291:189–193. doi: 10.1016/j.jccard.2019.02.007