Anatomical characteristics of anomalous left coronary artery from the opposite sinus (left-ACAOS) and its clinical relevance: A serial coronary CT angiography study

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Abstract

Background: Anomalous left coronary artery from the opposite sinus (left-ACAOS) is a rare congenital heart disease. While “interarterial course” is considered as the malignant anatomic feature for these patients, a number of patients with left-ACAOS, who don’t follow the above anatomic pattern, were reported with ischemic symptoms.

Purpose: This study aims to evaluate the anatomic characteristics of left-ACAOS and their clinical relevance.

Methods: The coronary computed tomography angiography (CCTA) data from 44 patients with 46 left-ACAOS vessels were retrospectively included. Patients were divided into 2 groups: those with ischemic symptoms (n = 19) and those without ischemic symptoms (n = 25). Baseline clinical characteristics were recorded and the follow-up was done by telephone. CCTA images were reviewed for anomalous coronary artery, take-off angle and level, ostia morphology and grading, proximal narrowing, anomalous course and atherosclerotic plaques.

Results: The prevalence of left-ACAOS was approximately 0.09% among 48,719 consecutive patients referred for coronary CTA in our institution. Right sinus of Valsalva (RSV) was the most common origin (36/46, 78.26%). Left-ACAOS arising from right coronary artery (RCA) had narrower proximal segment (P = 0.014) and more prone to atherosclerosis (P = 0.040) than left-ACAOS arising from right sinus of Valsalva (RSV). Proximal narrowing severity (P < 0.001) and degree of maximal coronary stenosis (P = 0.034) of the anomalous left artery was higher in patients with ischemic symptoms than those without. Of note, no MACE was recorded during a mean follow-up of 43.4 ± 26.2 months.

Conclusion: Left-ACAOS arising from RCA seems to be more prone to atherosclerosis than other subtypes. Proximal narrowing was more severe in patients with ischemia symptoms, which may contribute to risk stratification and clinical management.

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1. Introduction

Anomalous left coronary artery from the opposite sinus (left-ACAOS) is a rare congenital heart disease with a broad spectrum of clinical presentations, from asymptomatic to ischemic symptoms and even sudden cardiac death (SCD) [1]. Left-ACAOS with an interarterial course is considered as a malignant variant, and surgery is recommended for this pattern [2]. However, a number of left-ACAOS patients who do not experience an interarterial course also present with ischemic symptoms [1,3], and management of these patients remains controversial. Identifying all factors associated with ischemia symptoms potentially influences decisions about selecting an effective treatment measures and appropriate exercise intensity. Coronary computed tomography angiography (CCTA) is an acute, noninvasive technique for assessing anatomic structural features of the anomalous coronary artery [4] and coronary artery disease [5].
Moreover, invasive coronary angiography involving anomalous coronary arteries is challenging due to their unusual location and course [6]. Nevertheless, detailed descriptions of the automatic features of left-ACAOS are limited to case reports and small sample studies due to the rarity of the disease. Improved data regarding the variable characteristics in the origin of the coronary artery and its anatomic patterns might help in selecting the appropriate catheters for diagnostic and therapeutic intervention.

In the present study, we aimed to evaluate (1) the prevalence of left-ACAOS among patients referred for CCTA and anatomic features with different anomalous origin; (2) the association between CCTA-identified coronary features and ischemia symptoms; (3) the incidence of main adverse cardiac events (MACEs).

2. Methods

2.1. Patient selection

All patients (48,719) referred to our institution for CCTA between January 2012 and August 2019 were retrospectively screened for the study. Patients underwent CCTAs for suspected CAD, preoperative evaluation or screening of CAD, except for one patient with coronary angiogram and suspected coronary anomaly. Patients diagnosed with left-ACAOS by CCTA were identified. The exclusion criteria included the following: (1) patients with complex congenital heart disease or any severe valvular heart disease. Complex congenital heart disease was defined as congenital heart defect that could cause hemodynamics disorders such as transposition of the great artery. Severe valvular heart disease was defined based on the ACC/AHA 2017 guidelines for the management of patients with valvular heart disease [7]; (2) patients had a prior revascularization; (3) CCTA images with poor quality that cannot be measured due to obvious artifact. All subjects enrolled were divided into 2 groups according to ischemic symptoms (ischemic symptoms and no ischemic symptoms groups). Ischemic symptom was defined as a composition of chest pain, palpitation, shortness of breath and arrhythmia. Informed consent was obtained before CCTA. This single-center study was approved by the institutional review boards of our hospital and was conducted in accordance with institutional guidelines. Information on demographic variables and clinical characteristics on admission were collected through a review of electronic medical records and patient questionnaires.

2.2. CCTA scanning protocols

All CCTA scans were performed using a Dual Source CT scanner (Somatom Definition Flash; Siemens Medical Solutions, Forchheim, Germany) according to established guidelines [8]. Sedation was not used. Patients were in the supine position and a retrospective electrocardiography (ECG)-gated protocol was used to eliminate cardiac motion artefacts. Scanning parameters were set as follows: tube voltage was set as 100–120 kV (adapted to body mass index); tube current, 220 mAs; collimation, 64 × 0.6 mm; gantry rotation time, 0.33 s; pitch, 0.2–0.5 (adapted to heart rate). CCTA images were acquired during breath-holding period to eliminate breath- holding artefacts. Nonionic contrast agent (iopamidol, 370 mg/ml, Bracco, Milan, Italy) was injected into an antecubital vein at a flow rate of 5 ml/s (70–90 ml, adapted to body mass index) and saline solution (20 ml) was injected at the same flow rate 20 min later.

2.3. CCTA image reconstruction and analysis

CCTA images were transferred to an image analysis work stat (Horos, V3.3.1) and reconstructed with a slice thickness of 0.75 mm and an increment of 0.7 mm. To avoid bias and ensure consistency of measurements, all CCTA studies were independently reviewed by two experienced radiologists (at least 2 years of CCTA experience) blinded to the clinical parameters. Any discrepancies in the interpretations of the two observers were resolved by consensus or consulting with a superior radiologist with 30 years of CCTA experience.

All the CCTA images were visualized by multiplanar reformations and 3-dimensional volume-rendered images for the presence of coronary anatomy characteristics and atherosclerosis. The diagonal branches, obtuse marginal branches, and posterolateral branches were considered part of the left anterior descending coronary artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA) system, respectively.

Since anomalous origin was reported to be instructive for surgery [9], we investigated the anatomical characteristics of left-ACAOS based on its origin: left-ACAOS arising from right sinus of Valsalva (RSV), RCA and noncoronary sinus of Valsalva (NSV). We examined anatomic characteristics of anomalous vessels, including the ostia grading, ostia morphology, take-off level, take-off angle, proximal narrowing and anomalous courses.

Ostia grading is a four-level grading system [10] which is used to describe the ostia when two vessels are in close proximity to each other: separate ostia, adjacent ostia, shared ostia and branch vessel. Another type is the anomalous coronary artery arising alone from NSV (Fig. 1). Ostia morphology is determined by the ratio of transverse diameter and antero-posterior (AP) diameter of the ostia of the anomalous coronary artery [11]. The ostia morphology of the anomalous coronary artery was classified as follows: if the ratio >90%, the ostia morphology was defined as normal; ratio = 50–90%, oval; and ratio <50%, slit-like change (Fig. 2). Take-off level is categorized as at/above or below the aortic valve commissure. Take-off angle is defined as the angle between the plane along the centerline of the blood vessel perpendicular to the center of the ostium and the plane tangent to the aorta, which was in the same direction as the coronary artery [10]. Take-off angle <45° was recorded as acute take-off angle. Proximal course is classified as follows [11]: the proximal coronary artery traveling anterior to the pulmonary valve was defined as the prepulmonic course; below the level of the pulmonary valve annulus, subpulmonic course; between the aorta and the pulmonary artery, interarterial course; and posterior to the aorta, retroaortic course. Intramural course is defined as coronary artery traveling within the aortic wall [12], with the absence of adjacent epicardial fat (tissue region of interest mean signal < 30 Hounsfield Units) [13]. Intramycardial course, including intracaval and intraseptal course, is defined as any artery segment that ran intramurally, surrounded by at least 1 mm of myocardium in the CCTA images [14]. Proximal narrowing is defined as the most narrowed location with distal normal vessels as reference [10], in the exclusion of atherogenic causes. Centerline length of vessel narrowing extending from the most proximal segment to the normal caliber distal reference was recorded as the length of narrowing (Fig. 3).

Finally, we estimated the prevalence and stenosis severity of atherosclerosis in both anomalous and normal coronary arteries. Coronary atherosclerosis was defined as tissue structures >1 mm² that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [15]. Coronary atherosclerotic plaques were quantified for stenosis according to the 5-point CAD-RAD grading scale [16]; if there was no plaque or stenosis, it was recorded as Grade 0; ≤25% luminal stenosis, Grade 1; 25–50% luminal stenosis, Grade 2; 50–70% luminal stenosis, Grade 3; 70–99% luminal stenosis, Grade 4; totally occluded, Grade 5. Coronary luminal stenosis ≥50% was recorded as obstructive coronary artery disease (CAD). Only coro-
nary segment with a >1.5 mm diameter was evaluated for CAD-RAD grading.

The above CCTA characteristics were assessed at per-vessel and per-patient level. For per-vessel analysis, degree of maximal luminal stenosis in studied coronary arteries was recorded. For per-patient analysis, the smallest take-off angle, degree of maximal proximal narrowing, longest length of proximal narrowing and degree of maximal luminal stenosis due to atherosclerosis were recorded for patients with multiple anomalous coronary arteries.

### 2.4. CCTA radiation dose estimation

The volume CT dose index (CTDI) and dose-length product (DLP) were collected from the dose report. The effective dose (ED) was calculated by multiplying DLP by a conversion factor (k-factor = 0.014 mSv\cdot mGy\(^{-1}\cdot cm\(^{-1}\)) based on previous guidelines [17,18].

### 2.5. Follow-up

Follow-up was obtained via telephone contact, clinical visits or medical records for cardiac events by a researcher who was blinded to the CCTA results. The endpoint was a composite of MACES, including all-cause mortality, heart failure, significant arrhythmia, syncope or urgent/non-urgent revascularization. Significant arrhythmia was defined as the arrhythmia that causes hemodynamic disorder in a short period of time, leading to syncope and even sudden death in patients.

### 2.6. Statistical analysis

The data are presented as means ± standard deviation (SD) for continuous variables with a normal distribution, as medians (interquartile range) for continuous variables with a nonnormal distribution, and as frequency (%) for categorical variables. The

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**Fig. 1. Ostia grading.** Left-ACAOS, anomalous left coronary artery from the opposite sinus; NSV, non-coronary sinus of Valsalva.
Fig. 2. Ostia morphology, take-off angle, take-off level, and anomalous courses. (a) Transverse diameter and antero-posterior diameter of the left-ACAOS ostia were obtained in double oblique view using the smallest available slice thickness (0.75 mm). (b). Take-off angle was obtained between the plane along the centerline of the blood vessel perpendicular to the center of the ostium and the plane tangent to the aorta in the same direction as the coronary artery. (c) Take-off level was evaluated based on the level of aortic valve. (d) Anomalous courses were obtained in multiplanar axial reconstructions using the smallest available slice thickness (0.75 mm).
The Kolmogorov–Smirnov test was used to assess normal distribution. Student’s t-test was used to compare continuous variables with normal distributions. The Mann–Whitney U test was employed for continuous variables with nonnormal distributions. The Pearson x² test or Fisher’s exact test was used to compare categorical variables. To determine the CCTA characteristics associated with ischaemic symptoms, logistic regression analysis was performed. Variables with P-values <0.1 in univariate analysis and potential high-risk characteristic were entered into the multivariable model. The inter- and intraobserver variabilities for reproducibility were evaluated using the intraclass correlation coefficient (ICC) and Bland-Altman plots. A 2-tailed P-value of <0.05 was considered statistically significant. All statistical analysis was performed using SPSS 25.0.

3. Results

3.1. Basic characteristics

Forty-five (0.09%) patients with left-ACAOS were identified, including 35 patients with left-ACAOS arising from RSV, 7 from RCA and 3 from NSV. One patient was excluded from the analyses due to the presence of complete congenital complete transposition of the great arteries. The remaining 44 patients (M/F: 20/24, 60.18 ± 13.06 years old) with 46 anomalous coronary arteries were enrolled (2 patients presented with anomalous LAD and LCx originating separately from RSV/RCA) (Table 1). Of the 44 patients, 43 (97.73%) were newly diagnosed with left-ACAOS. The mean CTDI, DLP and ED were 19.53 ± 17.43 mGy, 329.07 ± 291.03 mGycm, and 4.56 ± 4.08 mSv, respectively, remaining within the suggested range [19].

CCTA-identified ACAOS subtypes and their prevalence are demonstrated in Fig. 4. Out of the 46 left-ACAOS vessels, the most common anomalous origin was the right sinus of Valsalva (36/46, 78.26%), followed by the right coronary artery (7/46, 15.22%). The

![Fig. 3. Proximal narrowing.](image)

(a) Lumen diameters at the most narrowed location were obtained with distal normal vessels as reference using the smallest available slice thickness (0.75 mm). (b) Centerline length of proximal narrowing extending from the most proximal segment to the normal caliber distal reference was measured in multiplanar axial reconstructions using the smallest available slice thickness (0.75 mm).

**Table 1** Baseline characteristics.

| Characteristic                        | N = 44 |
|--------------------------------------|--------|
| Age (years)                          | 60.18 ± 13.06 |
| Sex                                  |        |
| Female                               | 24 (55.55%) |
| Male                                 | 20 (45.45%) |
| **Ischemic symptoms on admission**   |        |
| Chest pain                           | 13 (29.55%) |
| Shortness of breath                  | 13 (29.55%) |
| Palpitation                          | 9 (20.45%)  |
| Arrhythmia                           | 3 (6.82%) |
| **Newly diagnosed left-ACAOS**       | 43 (97.73%) |
| **Origin**                           |        |
| RSV                                  | 36/46 (78.26%) |
| RCA                                  | 7/46 (15.22%) |
| NSV                                  | 3/46 (6.52%)  |
| **Congenital heart disease**         | 2 (4.55%) |
| Atherosclerosis                      | 25 (56.82%) |
| Obstructive CAD                      | 7 (16.28%) |
| MACE<sup>a</sup>                     | 2 (4.55%) |

Data are expressed as n (%) or mean ± SD. RSV, right sinus of Valsalva; RCA, right coronary artery; NSV, non-coronary sinus of Valsalva; MACE, main adverse cardiac events.

<sup>a</sup> Note: % don not sum to 100% as some patients had multiple symptoms on admission.

<sup>b</sup> Cardiac mortality, heart failure, significant arrhythmia, syncope or urgent/non-urgent revascularization.
most common anomalous artery was LCx (24/46, 52.17%), followed by LM (19/46, 41.30%) and LAD (3/46, 6.52%). Notable, all of the 7 anomalous arteries with interarterial course were LM. Twenty-six patients had a retroaortic course (26/46, 56.52%), for which LCX was the most common anomalous artery (23/26, 88.46%).

3.2. CCTA findings in left-ACAOS subtypes

CCTA characteristics of 46 anomalous left coronary arteries were presented in Table 2, stratified by their anomalous origin. When compared to left-ACAOS arising from RSV, the frequency of atherosclerosis was more common in left-ACAOS arising from RCA ($P = 0.04$), accompanied by more severe luminal stenosis ($P = 0.030$) and narrower proximal segment ($P = 0.014$) (Fig. 5a). Fig. 5b showed the percentage of atherosclerosis in left-ACAOS subtypes. The percentage of atherosclerosis in LM arising from RCA was 100% (1/1); LCx arising from RCA, 60% (3/5); LAD arising from RSV, 50% (1/2).

Additionally, there was no significant difference with regard to the prevalence of atherosclerosis (10/46 vs. 32/130, $P = 0.694$) or degree of maximal luminal stenosis ($P = 0.424$) in anomalous coronary arteries compared with normal coronary arteries.

3.3. Clinical symptoms relevance of CCTA-identified characteristics

Of the 44 patients, 19 (43.18%) were reported with ischemic symptoms. Compared to patients without ischemic symptoms, patients with symptoms had a more severe degree of maximal coronary stenosis ($P = 0.004$) in anomalous coronary arteries, without significant differences in the prevalence ($P = 0.888$) or degree of maximal coronary stenosis ($P = 0.894$) of normal coronary atherosclerosis (Table 3). Proximal narrowing severity of the anomalous left artery was higher in patients with ischemic symptoms than in those without ($P < 0.001$). There were no significant differences in the prevalence of slit-like ostia, take-off angle, interarterial course, subpulmonic course, intramural course or intramyocardial course between these two groups ($all P > 0.05$).

Of note, no MACE was recorded during a mean follow-up of 43.4 ± 26.2 months.

3.4. Inter- and intraobserver variability

There was excellent inter- and intraobserver variability for consecutive parameters including take-off angle, degree and length of

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**Table 2**

| Variable | Left-ACAOS arising from RSV (n = 36) | Left-ACAOS arising from RCA (N = 7) | Left-ACAOS arising from NSV (N = 3) |
|----------|-------------------------------------|-----------------------------------|----------------------------------|
| Anomalous coronary artery | | | |
| LM | 16 (44.44%) | 1 (14.28%) | 2 (66.67%) |
| LAD | 2 (5.56%) | 1 (14.28%) | 0 |
| LCx | 18 (50.00%) | 5 (71.43%) | 1 (33.33%) |
| Ostia morphology | | | |
| Normal ostia | 10 (27.78%) | 6 (85.71%) | 0 |
| Oval ostia | 25 (69.44%) | 1 (14.28%) | 2 (66.67%) |
| Slit-like ostia | 1 (2.78%) | 0 | 1 (33.33%) |
| % Proximal narrowing (Amin diameter) | 20.28 ± 15.87 | 25.09 ± 26.95 $^*$ | 35.57 ± 20.66 |
| Length of narrowing (mm) | 4.45 ± 2.92 | 5.86 ± 1.97 | 4.20 ± 1.47 |
| Take-off angle (°) | 53.71 ± 29.91 | 56.03 ± 34.85 | 39.75 ± 38.65 |
| Take-off level at above commissure | 1 (2.78%) | 0 | 0 |
| Proximal courses | | | |
| Interarterial course | 6 (16.67%) | 1 (14.28%) | 0 |
| Subpulmonic course | 4 (11.11%) | 1 (14.28%) | 0 |
| Prepulmonic course | 8 (22.22%) | 0 | 0 |
| Retroaortic course | 18 (50.00%) | 5 (71.43%) | 3 (100.00%) |
| Intramyocardial course | 12 (33.33%) | 1 (14.28%) | 0 |
| Intramural course | 2 (5.56%) | 0 | 1 (33.33%) |
| Atherosclerosis | 6 (16.67%) | 4 (57.14%) $^*$ | 0 |
| Degree of maximal luminal stenosis | | | |
| 0 | 32 (88.89%) | 3 (42.86%) $^*$ | 3 (100.00%) |
| 1 | 0 | 2 (28.57%) | 0 |
| 2 | 0 | 2 (28.57%) | 0 |
| 3 | 4 (11.11%) | 0 | 0 |

Anomalous coronary artery-level analysis. Data are expressed as n (%) or mean ± SD. CCTA, Coronary computed tomography angiography; left-ACAOS, anomalous left coronary artery from the opposite sinus; RSV, right sinus of Valsalva; RCA, right coronary artery; NSV, non-coronary sinus of Valsalva; LM, left main coronary; LAD, left anterior descending coronary artery; LCx, left circumflex artery.

$^*$ $P < 0.05$ versus left-ACAOS arising from RSV.
proximal narrowing (ICC = 0.850–0.997) (Table 4). The Bland-Altman plots of intra- and inter-observer agreement were displayed in Supplementary Fig. 1.

4. Discussion

This study took a close look at the anatomic features on CCTA, as well as its clinical relevance, by simultaneously analyzed the ischemia symptoms and MACE as the outcome. The main findings of our study were as follows: (1) the prevalence of left-ACAOS was 0.09% among patients referred for CCTA; (2) left-ACAOS arising from RCA were more prone to develop atherosclerosis and had narrower proximal segment than other left-ACAOS subtypes; (3) proximal narrowing and atherosclerosis stenosis in anomalous coronary arteries might be relevant to ischemic symptoms.

Cheezum et al. [20] examined anatomical characterization and its association with coronary revascularization in ACAOS patients undergoing CTA, observing that length and proximal vessel narrowing were associated with coronary revascularization, which suggested that CCTA provides a comprehensive anatomical assessment of ACAOS vessels for clinical management. Notably, their study revealed a low incidence of interarterial course compared with right-ACAOS. Considering that interarterial course is a risk factor recommended for coronary revascularization based on published guidelines [21,22], patients with coronary revascularization may be primarily right-ACAOS patients in their study, and therefore, the results would be more suitable for patients with right-ACAOS. Moreover, although the prevalence of left-ACAOS is lower than right-ACAOS, the high occurrence of SCD in left-ACAOS should not be neglected. Nevertheless, studies focused on anatomic characteristics and its clinical relevance in left-ACAOS are limited to case reports and small sample studies due to the rarity of this condition. Improved data on left-ACAOS may provide more detailed information for management of these patients. Additionally, considering the limitation of invasive coronary angiography for detecting the initial course of left-ACAOS in diagnostic/therapeutic assessment [23], a detailed description of the anatomic characteristics of the subtypes of this disease based on their origin is required.

4.1. Prevalence of left-ACAOS among patients referred for CCTA

The prevalence of left-ACAOS in patients referred for CCTA in this study was lower than 0.62% in a previous study [24]. Our study further documented in detail the prevalence of the various subtypes of left-ACAOS. The prevalence of anomalous left coronary artery originating from RCA and RSV was 0.02% and 0.09%, respectively, consistent with previous studies (<0.02–0.05% [25] and <0.1% [26], respectively). The prevalence of anomalous left coronary artery originating from NSV was relatively low as well (0.01%). However, because we reported a referred rather than a screening population, the true prevalence of left-ACAOS and its subtypes in the general population remains to be determined in future studies. In addition, previous studies [27,28] demonstrated that the anomalous aortic origin of a coronary artery was familial clustering; therefore, it is reasonable to suggest that large sample and multicenter studies are needed to confirm whether the incidence of left-ACAOS is racially or regionally affected.

Interestingly, we found that the anomalous LM and LAD accounts for half of the abnormal left coronary arteries, and a higher prevalence of interarterial course of LM was noted. The blood supply area of the left trunk and left anterior descending branch is larger. This may explain why there is a lower incidence of left coronary abnormalities but a higher incidence of right coronary abnormalities in patients with sudden death [29]. Large prospective studies are warranted to focus on the outcomes in patients with anomalous LM or LAD.

4.2. Left-ACAOS arising from RCA had higher prevalence and stenosis of atherosclerosis with proximal narrowing

Among anomalous coronary arteries, left-ACAOS arising from RCA seemed to be predisposed to atherosclerosis with narrower proximal segment. This is likely due to proximal narrowing potentially increasing endothelial shear stress [30], and the tangential force exerted on the vessel wall is attributed to the friction of blood flow on the endothelial surface [28,31], leading to the susceptibility to atherosclerosis in left-ACAOS arising from RCA. This might indicate a population that is at higher risk for coronary atherosclerosis, and who require more careful assessment and consideration for monitoring. Moreover, the more severe degree of proximal nar-
rowing of left-ACAOS arising from RCA might be instructive for the selection of catheters [9].

Disputes exist regarding the incidence of atherosclerosis between the anomalous and non-anomalous coronary arteries. Suryanarayana et al.'s [32] and Gräni's et al.'s [33] studies showed no significant difference in the occurrence and severity of atherosclerosis between normal and anomalous coronaries, using invasive angiography and CCTA respectively. However, Navdeep Singh Sidhu et al. [34] showed that significant CAD involvement was more frequent in anomalous vessels than anomalous vessels in patients with coronary artery anomalies undergoing catheter coronary angiography. A coronary angiography study by Samarendra et al. [35] showed earlier and greater degree of atherosclerosis in patients with anomalous LCx in comparison with normal coronaries in the same patients and nonanomalous LCx in a gender matched control subjects. Herein, the incidence and stenosis severity of atherosclerosis were similar between anomalous and normal coronary arteries.

### Table 3
Clinical and CCTA-identified characteristics of patients stratified by ischemic symptoms.

| Variable                                      | All (N = 44) | Ischemic symptoms (N = 19) | No ischemic symptoms (N = 25) | P     |
|-----------------------------------------------|--------------|---------------------------|------------------------------|-------|
| Age (years)                                   | 60.18 ± 13.06| 58.10 ± 16.35             | 61.76 ± 9.96                 | 0.161 |
| Male                                          | 20 (45.45%)  | 11 (57.89%)               | 9 (36.00%)                   | 0.223 |
| Anomalous coronary artery                     |              |                           |                              |       |
| LM                                            | 19 (41.30%)  | 10 (52.63%)               | 8 (32.00%)                   | 0.888 |
| LAD                                           | 3 (6.52%)    | 1 (5.26%)                 | 2 (8.00%)                    | 0.721 |
| LCx                                           | 24 (52.17%)  | 13 (68.42%)               | 11 (44.00%)                  | 0.766 |
| Anomalous origin                              |              |                           |                              |       |
| RSV                                           | 36 (81.82%)  | 15 (78.95%)               | 21 (84.00%)                  | 0.467 |
| RCA                                           | 7 (15.91%)   | 3 (15.79%)                | 4 (16.00%)                   | 0.985 |
| NSV                                           | 3 (6.82%)    | 2 (10.33%)                | 1 (4.00%)                    | 0.570 |
| Ostia grading                                 |              |                           |                              |       |
| Separate ostia                                | 8 (18.18%)   | 3 (15.79%)                | 5 (20.00%)                   | 0.720 |
| Adjacent ostia                                | 14 (31.82%)  | 11 (57.89%)               | 3 (12.00%)                   | 0.058 |
| Shared ostia                                  | 14 (31.82%)  | 7 (36.84%)                | 7 (28.00%)                   | 0.745 |
| Branch vessel                                 | 7 (19.57%)   | 3 (15.79%)                | 4 (16.00%)                   | 0.985 |
| Ostia morphology                              |              |                           |                              |       |
| Normal ostia                                  | 15 (34.09%)  | 8 (42.11%)                | 7 (28.00%)                   | 0.357 |
| Oval ostia                                    | 25 (56.82%)  | 16 (84.21%)               | 9 (36.00%)                   | 0.361 |
| Slit-like ostia                               | 2 (4.55%)    | 2 (10.53%)                | 0                            | 0.181 |
| % Proximal narrowing (Amin diameter)          | 20.64 ± 17.28| 26.90 ± 22.69             | 15.88 ± 6.95                 | <0.001|
| Length of narrowing (mm)                      | 4.64 ± 2.76  | 4.47 ± 2.44               | 4.76 ± 3.03                  | 0.699 |
| Take-off angle (°)                            | 50.61 ± 30.01| 58.71 ± 29.19             | 50.72 ± 31.36                | 0.736 |
| Take-off level at/above commissure            | 1 (2.27%)    | 1 (5.26%)                 | 0                            | –     |
| Proximal courses                              |              |                           |                              |       |
| Interarterial course                          | 7 (15.91%)   | 3 (15.79%)                | 4 (16.00%)                   | 0.985 |
| Subpulmonic course                            | 5 (11.36%)   | 2 (10.53%)                | 3 (12.00%)                   | 0.879 |
| Prepulmonic course                            | 8 (18.18%)   | 4 (21.05%)                | 4 (16.00%)                   | 0.667 |
| Retroaortic course                            | 26 (59.09%)  | 11 (57.89%)               | 15 (60.00%)                  | 0.888 |
| Intramural course                             | 3 (6.82%)    | 1 (5.26%)                 | 2 (8.00%)                    | 1.000 |
| Intramyocardial course                        | 13 (2.72%)   | 4 (21.05%)                | 9 (36.00%)                   | 0.324 |
| Atherosclerosis in anomalous coronary arteries | 10 (20.45%)  | 7 (36.84%)                | 3 (12.00%)                   | 0.074 |
| Degree of maximal coronary stenosis in anomalous coronary arteries | | | | | | 0 | 36 (88.63%) | 13 (68.42%) | 23 (92.00%) | 0.034 |
| 1                                             | 2 (4.55%)    | 1 (5.26%)                 | 1 (4.00%)                    |       |
| 2                                             | 2 (4.55%)    | 1 (5.26%)                 | 1 (4.00%)                    |       |
| 3                                             | 4 (9.09%)    | 4 (21.05%)                | 0                            |       |
| Atherosclerosis in normal coronary arteries    | 18 (40.91%)  | 8 (42.11%)                | 10 (%)                       | 0.888 |
| Degree of maximal coronary stenosis in normal coronary arteries | | | | | | 0 | 26 (59.09%) | 11 (%) | 15 (50.00%) | 0.894 |
| 1                                             | 5 (11.36%)   | 2 (%)                     | 3 (12.00%)                   |       |
| 2                                             | 9 (20.45%)   | 6 (%)                     | 3 (12.00%)                   |       |
| 3                                             | 3 (6.82%)    | 0                         | 3 (12.00%)                   |       |
| 4                                             | 1 (2.27%)    | 0                         | 1 (4.00%)                    |       |
| LCA dominance                                 |              |                           |                              |       |
| RCA/AAO                                       |              |                           |                              |       |

Patient-level analysis. Data are expressed as n (%) or mean ± SD. CCTA, Coronary computed tomography angiography; left-ACAOS, anomalous left coronary artery from the opposite sinus; LM, left main coronary; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RSV, right sinus of Valsalva; RCA, right coronary artery; NSV, non-coronary sinus of Valsalva.

* Note: % don not sum to 100% as some patients had multiple anomalous coronary arteries.

### Table 4
Inter- and intra-observer variability of take-off angle, proximal narrowing severity and length.

| Variable                                      | Inter-observer (n = 46) | Intra-observer (n = 46) |
|-----------------------------------------------|------------------------|------------------------|
|                                               | ICC 95% CI              | ICC 95% CI              |
| Take-off angle                                | 0.996 0.992–0.998      | 0.997 0.994–0.998      |
| % Proximal narrowing                          | 0.986 0.975–0.992      | 0.995 0.991–0.997      |
| Length of narrowing                           | 0.906 0.836–0.947      | 0.850 0.854–0.955      |

ICC, intraclass correlation coefficient.
4.3. Proximal narrowing and its association with clinical symptoms

“Interarterial course” is considered as the malignant anatomic feature for left-ACAOS patients [36], which could induce transient myocardial ischemia [37], thus conferring an increased risk of a malignant prognosis. Paradoxically, a number of patients with left-ACAOS, who didn't follow the above anatomic pattern, were reported with ischemic symptoms. Additionally, most of the patients with the reported malignant anatomical features, even those with SCD, failed to show significant ischemia during stress testing [38]. For these reasons, the anatomically based approach for identifying patients at high risk for malignant prognosis has been advocated over the stress-induced ischemia-based approach in the diagnostic workup of left-ACAOS and requires further refinement. As a robust imaging method for anatomic delineation of anomalous coronary arteries [13], CCTA was used in this study to explore the anatomical features associated with clinical presentation.

In addition to “interarterial courses”, some additional potential high-risk coronary artery abnormalities are typically demonstrated in patients with ischemia in ACAOS, including acute take-off angle [33], intraseptal course [39], intramural course and length, and orifice anomalies [40] etc., but no agreement has been reached concerning definite risk features. In our series, proximal narrowing exhibited a weak association with ischemic symptoms; this is in accordance with data in right-ACAOS patients from Opolski, et al.’s [24] and Marano et al.’s [41]. Consistently, Cheezum et al. [20] demonstrated that length and proximal vessel narrowing were associated with coronary revascularization in ACAOS patients undergoing CTA. These findings might be useful for risk stratification of these patients to ensure appropriate management. Further large prospective studies are required to validate the role of proximal narrowing.

5. Limitations

There are several limitations in this study. First, this was a single-center study with racially and regionally limitations. Future large multicenter studies should be encouraged. Second, due to the rarity of diagnosed left-ACAOS and the low frequency of presentation with SCD, this study was underpowered to confirm the high-risk characteristics of MACE. However, we enrolled patients referred for CCTA due to suspected cardiovascular disease retrospectively. Thus, these patients were more likely to experience clinical presentation compared to the general population. Third, patients referred for CCTA are generally adult and elderly patients and we would have missed a large proportion of pediatric and young adult patients, who were reported to be more at high-risk for SCD than older patients. Finally, due to the relatively short follow-up period, incidence of MACE may be underestimated. Therefore, we will continue to follow-up this cohort to confirm our conclusion.

6. Conclusions

Our study identified a high susceptibility to atherosclerosis in left-ACAOS arising from RCA compared to other left-ACAOS subtypes based on their origin. Attention should be paid to the risk for atherosclerosis in left-ACAOS arising from RCA. Moreover, we found that proximal narrowing severity and the degree of maximal luminal stenosis were more severe in patients with ischemic symptoms compared to those without ischemic symptoms. These findings may provide a basis for improved risk stratification and refinements to management. However, we caution that larger numbers of patients, including more pediatric and young adult patients, and longer follow-up times are needed to further validate these results.

Authorship statement

Pei-lun Han and Kai-yue Diao are mainly in charge of the manuscript writing and idea design. Shan Huang helped edit the table and figures, as well as the patient’s image analysis; Yue Gao, Ying-kun Guo and Ning Yang helped in data collection. Zhi-gang Yang takes responsibility of the study design, has full access to the data in the study and has the final responsibility to submit for publication.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100649.

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