

Features associated with myocardial ischemia in anomalous aortic origin of a coronary artery: A Congenital Heart Surgeons' Society study



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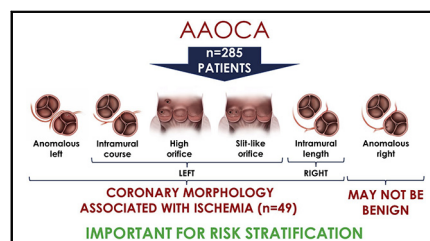
ABSTRACT

Objectives: We sought to determine anatomic features associated with evidence of myocardial ischemia and sudden cardiac events (arrest or death) for patients with anomalous aortic origin of a coronary artery.

Methods: We enrolled 560 patients, less than or equal to 30 years, at diagnosis from 40 institutions. Ischemia was defined as the presence of exertional syncope, a sudden cardiac event (arrest/death), or abnormal investigation results. Data on detailed anatomic features were abstracted from echocardiography, computed tomography, magnetic resonance imaging, operative, and/or surgeon-completed reports.

Results: There were 236 patients with negative ischemia test results, and 49 with evidence of ischemia (including 18 who presented with a sudden cardiac event); 275 asymptomatic patients who had not undergone provocative ischemia testing were excluded from primary analyses. Patients with ischemia (vs without), were more likely to have left anomalous coronary arteries (28/49 vs 46/236; $P < .0001$). Of patients with ischemia (vs without), those with anomalous left coronary arteries were more likely to have an intramural coronary artery course, or a high or slit-like coronary artery orifice. Of patients with ischemia (vs without), those with anomalous right coronary arteries were more likely to have a longer intramural course. Among patients with ischemia, the occurrence of sudden cardiac events was not shown to have any associated anatomic features.

Conclusions: Anatomic features including coronary artery involved, intramural course and length, and orifice anomalies were associated with evidence of myocardial ischemia for patients with anomalous aortic origin of a coronary artery. These features might importantly inform risk stratification and decisions regarding surgical management. (*J Thorac Cardiovasc Surg* 2019;158:822-34)



Primary findings related to myocardial ischemia in AAOCA.

Central Message

In anomalous aortic origin of a coronary artery, anomalous left coronary artery, intramural course, intramural length, and a high and/or slit-like orifice were associated with myocardial ischemia.

Perspective

Past studies of anomalous aortic origin of a coronary artery have been mainly autopsy and single institution series. We enrolled 560 patients, less than or equal to 30 years, with and without ischemia. Anomalous left coronary arteries, intramural course (presence and length), and high and/or slit-like orifice were associated with evidence of ischemia. These features might inform risk stratification and management.

See Commentary on page 835.

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Abbreviations and Acronyms

AAOCA	= anomalous aortic origin of a coronary artery
AAOLCA	= anomalous aortic origin of a left coronary artery
AAORCA	= anomalous aortic origin of a right coronary artery
CHSS	= Congenital Heart Surgeons' Society
SCA	= sudden cardiac arrest
SCD	= sudden cardiac death



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Anomalous aortic origin of a coronary artery (AAOCA) from the opposite sinus of Valsalva or with a high origin, which might have an interarterial, intramural, or intraconal course, is a rare congenital cardiac anomaly. It can be associated with myocardial ischemia (henceforth called ischemia) or sudden cardiac events (sudden cardiac arrest [SCA] or sudden cardiac death [SCD]).¹ Although most patients with AAOCA are diagnosed incidentally, others are diagnosed on the basis of their presenting symptoms.^{2,3} The prevalence of AAOCA is estimated to be between 0.01% and 2% of the population.⁴ However, there are an unknown number of individuals who have not been diagnosed because they are asymptomatic, and potentially have not experienced conditions sufficient to precipitate a sudden cardiac event. In addition, there are numerous anatomical variations on the basis of the individual components of a patient's morphology (coronary artery involved, its location, course, and ostial features). As such, it remains unknown which anatomic features or combinations of features can put a patient at risk for ischemia and/or sudden cardiac events.

Although multiple anatomic and physiologic theories have been proposed, the exact causes of ischemia and sudden cardiac events are likely multifactorial and require nuanced interpretation.⁵⁻¹² As such, risk stratification has proven difficult and surgical indications remain unclear. This is especially true in asymptomatic patients for whom one must determine if the risk of a sudden cardiac event is greater than the risk of an operation.^{4,13} Currently, the consensus guidelines only recommend an operation for those with ischemia or an interarterial left AAOCA

(AAOLCA).¹⁴ However, institutional and surgeon practices are highly varied.

In 2009, the Congenital Heart Surgeons' Society (CHSS) established this registry to clarify the natural and unnatural (surgically altered) history of AAOCA, including long-term outcomes, with the hope of informing risk stratification and management guidelines. The primary aims of the present study were to: (1) identify and compare the baseline characteristics of the entire cohort and the groups of interest (those with evidence of ischemia, with negative ischemia test results, with sudden cardiac events, and without sudden cardiac events), (2) characterize the best evidence of ischemia (most definitive) at presentation for patients with ischemia and sudden cardiac events, and (3) describe the anatomical features associated with evidence of ischemia and sudden cardiac events at presentation.

METHODS**Patients**

Patients were enrolled retrospectively (January 1, 1998 to January 20, 2009) and prospectively (January 21, 2009 to December 31, 2016) from 40 CHSS institutions. [Appendix E1](#) is a list of all enrolling institutions. Inclusion and exclusion criteria are listed in [Appendix E2](#). We have previously reported the registry design and implementation, cohort descriptions, surgical management, accuracy of echocardiographic evaluation, and the effect of exercise restriction on body mass index.^{2,15-19}

For this study, a patient was determined to have been tested for ischemia if he/she had undergone at least one provocative ischemia test. Provocative ischemia tests included cardiopulmonary exercise tests, stress echocardiograms, and nuclear perfusion scans. Patients were considered free of ischemia if they had undergone provocative testing and were found to be negative (henceforth called "patients without ischemia"). Patients were considered to have evidence of ischemia at diagnosis if they met the criteria described in [Table 1](#) (henceforth called "patients with ischemia"). Of note, chest pain without the additional findings of positive biomarkers or electrocardiographic changes did not meet criteria. Patients with ischemia were further assessed for occurrence of a sudden cardiac event at diagnosis. Patients with a sudden cardiac event at diagnosis are henceforth called "sudden cardiac event patients," and patients without a sudden cardiac event are henceforth called "nonsudden cardiac event patients." Thus, we created 4 primary groups of patients in this study for comparison: the patients without ischemia versus the patients with ischemia, and within the group of patients with ischemia, the sudden cardiac event patients versus nonsudden cardiac event patients.

Those who were untested and asymptomatic could not be accurately classified (henceforth called "unclassified patients"). They were not included with the patients without ischemia, because we believed that these patients likely included some patients with ischemia, who had not been discovered. A comparison of patients without ischemia versus unclassified patients was made to assess whether we appropriately excluded these patients.

Imaging and provocative testing were performed at the discretion of individual centers. These were not driven by registry-related protocols.

Data Collection and Aggregation of Anatomical Features

A description of data collection, and aggregation of anatomical features for each patient from multiple sources (echocardiogram, computed tomography, magnetic resonance imaging, surgical atomization) is provided in [Appendix E2](#). The atomization form used for collection of detailed morphologic data (used once for each study) is provided in the [Online Data Supplement](#).

Consent

Institutional review board approval was obtained for the CHSS (institutional review board approval number, initial study approval date, and expiration date: 1000014078, March 12, 2010, March 13, 2018), and at each participating site. Informed consent/assent was acquired from all patients or parents (when indicated) before enrollment. All institutional and patient participation was voluntary.

Statistical Analysis

Descriptive statistics were performed for the following groups: entire cohort, unclassified patients, patients without ischemia, patients with ischemia, sudden cardiac event patients, nonsudden cardiac event patients. Best evidence of ischemia and mode of presentation for patients with ischemia was determined. For the primary comparison groups (patients without ischemia vs patients with ischemia, sudden cardiac event patients vs nonsudden cardiac event patients), descriptive and comparative statistics were performed according to totals, AAOLCA and anomalous aortic origin of a right coronary artery (AAORCA) patients within each group. Finally, first and second surgical procedures were broken down into their individual components for patients with ischemia (eg, unroofing, reimplantation, etc). Standard statistics were performed using SAS 9.4 (SAS Institute, Cary, NC; Appendix E2).

RESULTS

A total of 560 patients were enrolled (131 retrospective, 429 prospective). This included 275/560 (49%) unclassified patients, 236/560 (42%) patients without ischemia, and 49/560 (9%) patients with ischemia. When we further reviewed the patients with ischemia for occurrence of sudden cardiac events, there were 31/49 (63%) nonsudden cardiac event patients, and 18/49 (37%) sudden cardiac event patients. Figure 1, A, depicts a flow diagram of patients in the cohort and the groups being compared. See Figure 1, B, for a flow diagram of the entire cohort

according to preoperative provocative testing, ischemia according to criteria at diagnosis, ischemia status, surgery, and coronary anatomy. A comparison of patients without ischemia and unclassified patients is shown in Table E1.

Baseline Characteristics and Ischemia Status

Baseline characteristics for the entire cohort and comparison groups are presented in Table 2. Several additional findings regarding the entire cohort and comparison groups are as follows. The proportion of African American patients with ischemia was significantly higher than that of other races (16/34 [47%] vs 35/131 [27%]; *P* = .02). Within the cohort with known ischemia status (236 patients without ischemia + 49 patients with ischemia = 285 patients) 3 findings were notable: (1) prevalence of ischemia was significantly lower among AAORCA patients compared with AAOLCA patients (10% [20/204] vs 38% [28/74]; *P* < .0001), (2) surgical intervention was common among all anomalies (55% [228/413] AAORCA, 67% [84/125] AAOLCA, and 63% [5/8] with both), and (3) of the 13/560 (2%) deceased patients in the cohort, mortality occurred with approximately equal frequency among AAOLCA (7 [54%]) and AAORCA (6 [46%]) patients.

Best Evidence of Ischemia at Presentation and Mode of Presentation for Patients With Ischemia and Sudden Cardiac Events

Table 3, section A describes the 49/285 (17%) patients in the cohort who met the criteria for ischemia, noting their coronary artery anatomy and best evidence of

TABLE 1. Criteria for ischemia

A. Presentation with any of the following events:
a. Sudden cardiac death and/or
b. Sudden cardiac arrest and/or
c. Requirement for cardiopulmonary resuscitation and/or
d. Requirement for preoperative extracorporeal mechanical oxygenation
OR
B. Presenting symptom of:
a. Syncope during or after exercise not explained as by dehydration or as a vasovagal event
OR
C. Preoperative or initial presentation with abnormal test:
a. Biomarkers (creatine kinase-muscle/brain or troponin I) above normal in the setting of congruent symptoms and/or
b. Ventricular tachycardia, infarction or ischemia on electrocardiogram in the same coronary artery territory as the anomalous coronary artery ²⁰ and/or
c. Abnormal cardiopulmonary exercise test with ST-segment changes in the same coronary artery territory as the anomalous coronary artery, exercise-induced hypotension, and/or significant arrhythmia (eg, ventricular tachycardia) ²¹
OR
D. Preoperative or initial presentation with abnormal imaging:
a. Abnormal perfusion scan with perfusion defect in the same coronary artery territory as the anomalous coronary artery and/or
b. Abnormal stress echocardiogram with wall motion abnormality in the same coronary artery territory as the anomalous coronary artery and/or
c. Abnormal magnetic resonance imaging with evidence of fibrosis or scar in the same coronary artery territory as the anomalous coronary artery and/or
d. Wall motion abnormalities in any modality with or without stress in the same coronary artery territory as the anomalous coronary artery

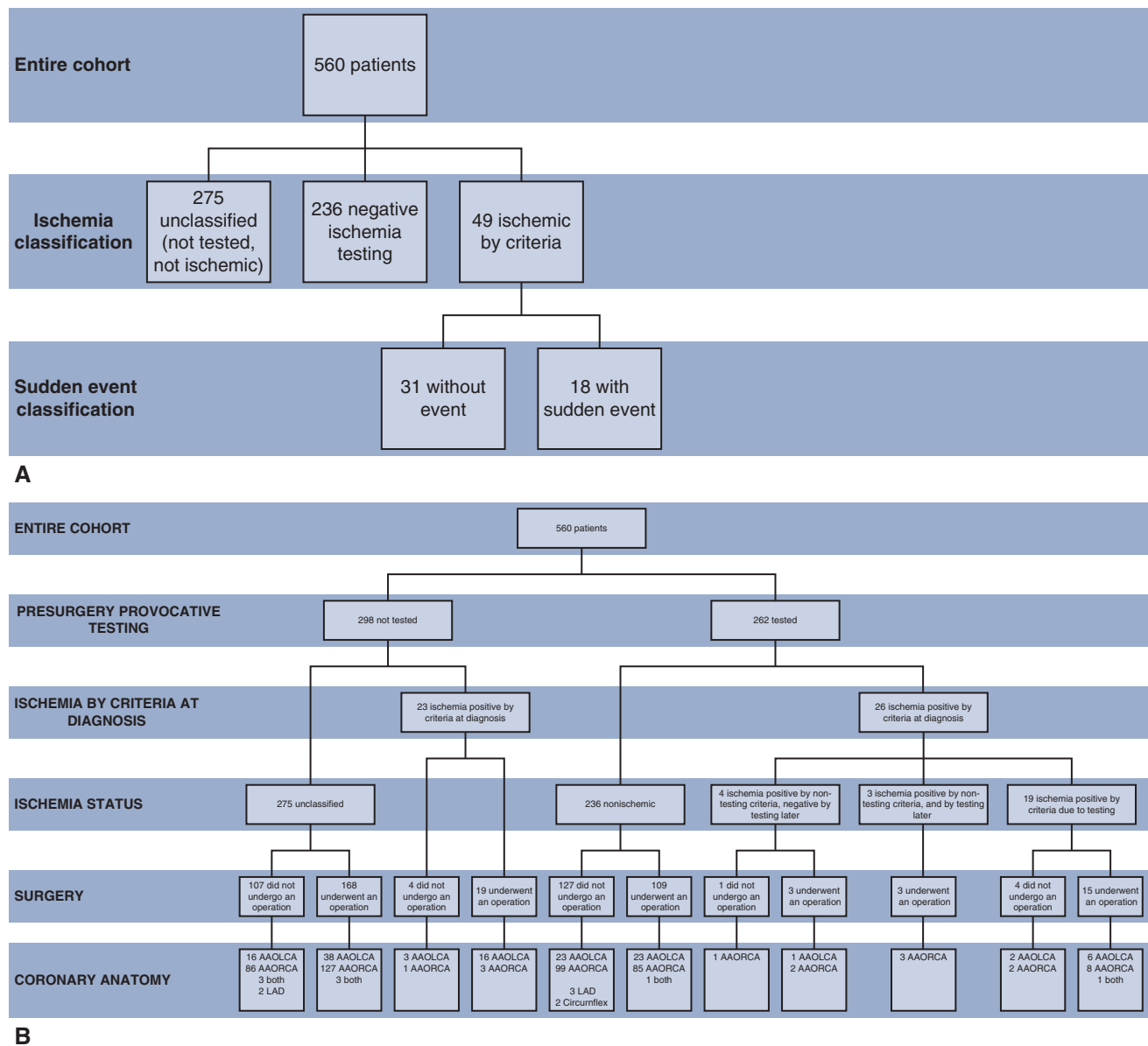


FIGURE 1. Flow diagram of patient classification in the cohort (N = 560). A, Flow diagram showing comparison of patients. B, Flow diagram of the entire cohort according to preoperative provocative testing, ischemia according to criteria at diagnosis, ischemia status, surgery, and coronary anatomy. AAOLCA, Anomalous aortic origin of a left coronary artery; AAORCA, anomalous aortic origin of a right coronary artery; LAD, left anterior descending.

ischemia at presentation. This includes the 18 patients who had a sudden cardiac event at presentation. Of the 49 patients, 12 presented because of some combination of symptoms/biomarkers/abnormal echocardiogram, 19 because of provocative testing, and 18 because of a sudden cardiac event (6 AAORCA, 12 AAOLCA). The distribution of sudden cardiac events among patients with AAORCA was 6/417 (1%), and for AAOLCA was 12/128 (9%).

Of patients with AAOLCA, the primary type of evidence was SCA (11/28; 39%). SCD occurred in only 1 patient with AAOLCA. Of patients with AAORCA, the 2 primary

types of evidence were abnormal nuclear perfusion stress test (30%), and SCA (30%). Of note, 1 patient with AAORCA and 3 with AAOLCA required mechanical circulatory support at the time of presentation.

Nearly all events in sudden cardiac event patients occurred with exertion (16/18; 89%). Of the 2 cases without exertion, 1 had AAORCA and 1 had both.

The most common mode of presentation for ischemic patients in our cohort (either AAOLCA or AAORCA) was SCA (Table 3, section B). Most of the remaining ischemic patients presented with symptoms, and several were found incidentally during screening echocardiography. The

TABLE 2. Baseline characteristics of entire cohort and patient groups

	All patients (N = 560)	Patients without ischemia (n = 236)	Patients with ischemia (n = 49)	Patients without vs patients with ischemia <i>P</i> value	Nonsudden cardiac event patients (n = 31)	Sudden cardiac event patients (n = 18)	Nonsudden cardiac event vs sudden cardiac event patients <i>P</i> value	Unclassified patients (n = 275)
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)		Median (IQR) or n (%)	Median (IQR) or n (%)		Median (IQR) or n (%)
Diagnosis age, y	11.6 (6.0-14.6)	12.7 (8.3-15.1)	13.5 (11.5-15.9)	.05	13.4 (9.4-16.1)	13.8 (12.8-14.9)	.6	9.0 (2.5-14.0)
Male sex	371 (66)	166 (70)	35 (71)	.9	23 (74)	12 (67)	.6	170 (62)
Race				.1			.4	
Caucasian	140 (47)	65 (50)	11 (32)		6 (30)	5 (36)		64 (47)
African American	92 (31)	35 (27)	16 (47)		9 (45)	7 (50)		41 (30)
Asian	12 (4)	8 (6)	0		0	0		4 (3)
Native American	2 (1)	1 (1)	0		0	0		1 (1)
Hispanic	43 (14)	16 (12)	4 (12)		4 (20)	0		23 (17)
Other	12 (4)	6 (5)	3 (9)		1 (5)	2 (14)		3 (2)
Missing	259 (46% of total)	105 (44% of total)	15 (31% of total)		11 (35% of total)	4 (22% of total)		139 (51% of total)
Anomalous coronary artery				<.0001			.7	
AAOLCA	128 (23)	46 (19)	28 (57)		16 (52)	12 (67)		54 (20)
AAORCA	417 (74)	184 (78)	20 (41)		14 (45)	6 (33)		213 (77)
LAD	5 (1)	3 (1)	0		0	0		2 (1)
Circumflex	2 (0.4)	2 (1)	0		0	0		0
Both*	8 (1)	1 (0.4)	1 (2)		1 (3)	0		6 (2)
Dead	13 (2)	2 (1)	5 (10)	.002	1 (3)	4 (22)	.05	6 (2)
Surgery	317/553 (57)	109/236 (46)	40/45 (89)	<.0001	25/30 (83)	15/15 (100)	1	168/272 (62)

In the surgical row, patients who died and were not eligible for surgery were removed from the denominator. *IQR*, Interquartile range; *AAOLCA*, anomalous aortic origin of a left coronary artery; *AAORCA*, anomalous aortic origin of a right coronary artery; *LAD*, left anterior descending. *Both denotes patients with AAOLCA and AAORCA.

proportion of patients among those with ischemia who were symptomatic was 29/49 (60%; 17 AAOLCA, 11 AAORCA, 1 both), with the remaining 20/49 (41%; 11 AAOLCA, and 9 AAORCA) asymptomatic.

Comparison of Patient Groups With Respect to Anatomical Features, Surgery, and Mortality

Table 4 provides the complete comparison of patients with ischemia (Table 4, section A) versus patients without ischemia (Table 4, section B). It also provides a comparison of sudden cardiac event patients (Table 4, section C) versus nonsudden cardiac event patients (Table 4, section D).

Within the known ischemia status group who had AAOLCA or AAORCA, ischemia was more common among AAOLCA patients than among AAORCA patients (38% [28/74] vs 10% [20/204]; *P* < .0001; Table 4, sections A and B). Conversely, there were more AAORCA patients among those without ischemia versus with ischemia (184/236 [78%] vs 20/49 [41%]; *P* < .0001; Table 4, sections A and B).

Compared with patients without ischemia who had AAOLCA, patients with ischemia who had AAOLCA were more likely to have an intramural course, high orifice, or slit-like orifice. Similarly, compared with patients without ischemia who had AAORCA, patients with ischemia who had AAORCA had a longer intramural course (Table 4, section B vs section A). Among the patients with ischemia, 48/49 (98%) patients had an interarterial course, and 43/49 (88%) had an intramural course (Table 4, section B). Of note, these proportions for patients without ischemia and nonsudden cardiac event patients were 93% and 97% interarterial, and 78% and 90% intramural, respectively. Of note, there were no patients with ischemia who had a prepulmonic course, and there were 2 AAOLCA patients with ischemia who had a retroaortic course.

There were no significant differences among sudden cardiac event patients versus nonsudden cardiac event patients, when the proportions of AAOLCA (12/18 [67%] vs 16/31 [52%]; *P* = .3), and AAORCA (6/18 [33%] vs

TABLE 3. Best evidence of ischemia at presentation and mode of presentation in 49 patients with ischemia

A. Best evidence of ischemia according to anomalous coronary artery		Patients, n (%)
AAOLCA (n = 28)		
Symptoms		4 (14)
Abnormal electrocardiogram, elevated biomarkers, symptoms		3 (11)
Abnormal echocardiogram		1 (4)
Abnormal exercise electrocardiogram		3 (11)
Abnormal stress echocardiogram		2 (7)
Abnormal nuclear perfusion stress test		3 (11)
Biomarkers, symptoms, preoperatively mechanical circulatory support		1 (4)
Symptoms, then sudden cardiac arrest with preoperative mechanical circulatory support		1 (4)
Sudden cardiac arrest (then preoperative mechanical circulatory support in 1 patient)		9 (32)
Sudden cardiac death		1 (4)
AAORCA (n = 20)		
Symptoms		2 (10)
Elevated biomarkers, and symptoms		1 (5)
Abnormal echocardiogram, elevated biomarkers, and symptoms		1 (5)
Abnormal exercise electrocardiogram		2 (10)
Abnormal stress echocardiogram		2 (10)
Abnormal nuclear perfusion stress test		6 (30)
Sudden cardiac arrest (then preoperative mechanical circulatory support in 1 patient)		6 (30)
Both (AAOLCA and AAORCA; n = 1)		
Abnormal nuclear perfusion stress test		1 (100)
B. Mode of presentation according to anomalous coronary artery		
AAOLCA (n = 28)		
Screening echocardiogram for hypertension		1 (4)
Exercise test for asthma with ST depressions		1 (4)
Palpitations		1 (4)
Shortness of breath and palpitations		1 (4)
Chest pain with activity		2 (7)
Syncope with activity		3 (11)
Syncope with activity and shortness of breath		1 (4)
Syncope with activity and chest pain		8 (29)
Syncope with activity and shortness of breath, and chest pain		1 (4)
Sudden cardiac arrest		9 (32)
AAORCA (n = 20)		
Screening echocardiogram for either: hypertension, murmur, family history of cardiomyopathy, WPW		4 (20)
Nausea, vomiting and hypotension with exercise		1 (5)
Chest pain		1 (5)
Chest pain and shortness of breath		2 (10)
Chest pain with exercise		1 (5)
Chest pain at rest		1 (5)

(Continued)

TABLE 3. Continued

B. Mode of presentation according to anomalous coronary artery	
Syncope with activity	1 (5)
Syncope with activity and palpitations	1 (5)
Syncope with activity and chest pain	1 (5)
Syncope with activity, shortness of breath, palpitations, and chest pain	2 (10)
Sudden cardiac arrest	5 (25)
Both (AAOLCA and AAORCA; n = 1)	
Syncope with activity	1 (100)

Lightest shading indicates symptoms/biomarkers/abnormal echocardiogram, medium shading indicates abnormal provocative ischemia testing, and darkest shading indicates sudden cardiac events. AAOLCA, Anomalous aortic origin of a left coronary artery; AAORCA, anomalous aortic origin of a right coronary artery; WPW, Wolff-Parkinson-White syndrome.

14/31 [45%]; $P = .4$) within each group were compared (Table 4, section D vs section C). There was also no difference in specific anatomic features when AAOLCA and AAORCA patients within the sudden cardiac event patients versus nonsudden cardiac event patients were compared (Table 4, section D vs section C).

There were more patients with ischemia who had AAOLCA versus patients without ischemia who had AAOLCA, who underwent operation (23/25 [92%] vs 23/46 [50%]; $P = .0004$). The same pattern was identified in patients with AAORCA (16/19 [84%] vs 85/184 [46%]; $P = .002$). A mortality difference was not found when patients with ischemia who had AAOLCA versus patients without ischemia who had AAOLCA were compared (4/26 [14%] vs 1/46 [2%]; $P = .06$). This was also the case for AAORCA patients (1/20 [5%] vs 1/184 [1%]; $P = .2$). See Table 4, section B versus Table 4, section A for the comparisons in this paragraph. There was a significantly greater proportion of sudden cardiac event patients who died (3 AAOLCA, 1 AAORCA) compared with nonsudden cardiac event patients who died (1 AAOLCA; 4/18 [22%] vs 1/31 [3%]; $P = .05$; Table 4, section D vs Table 4, section C).

Within the ischemic patients, there were 4 AAOLCA and 1 AAORCA patient who died. The 4 patients with AAOLCA died from either presumed or confirmed acute myocardial infarction. The patient with AAORCA died from heart failure secondary to a myocardial infarction. The diagnosis was made incidentally on autopsy.

Coronary Anatomy, Provocative Testing, and Evidence of Ischemia in Surgical Patients

Of the 317 surgical patients, 228 (228/317; 72%) had AAORCA, 84 (84/317; 26%) had AAOLCA, and 5 (5/317; 2%) patients had both. Previous preoperative provocative testing was performed in 130/317 (41%) patients. None of the patients in the cohort with isolated anomalous

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TABLE 4. Comparison of patient groups: patients without ischemia versus patients with ischemia, and nonsudden cardiac event patients versus sudden cardiac event patients

A. Patients without ischemia (n = 236)									
Anomalous coronary artery	Total	Dead	Surgery	Interarterial	Intramural	Intramural length, mm	High orifice	Slit-like orifice	
	N (%)	n (%)	n (%)	n (%)	n (%)	Median (IQR)	M, n	n (%)	n (%)
AAOLCA	46/236 (19)	1/46 (2)	23/46 (50)	34/41 (83)	18/35 (51)	7.5 (4.5-10)	5	2/32 (6)	10/28 (36)
AAORCA	184/236 (78)	1/184 (1)	85/184 (46)	158/161 (98)	114/131 (87)	6 (4.8-9)	38	44/105 (42)	62/81 (77)
LAD	3/236 (1)	0	0	0	0	0	0	0	0
Circumflex	2/236 (1)	0	0	1/2 (50)	0	0	0	0	0
Both	1/236 (0.4)	0	(1/1) 100	0	1/1 (100)	1.5	0	1/1 (100)	1/1 (100)
Total	236/236 (100)	2/236 (1)	109/236 (46)	193/208 (93)	133/170 (78)	6 (4.5-9)	43	47/140 (34)	73/111 (66)
B. Patients with ischemia (n = 49)									
AAOLCA	28/49 (57)	4/28 (14)	23/25 (92)	27/28 (96)	24/28 (86)	7 (3-10)	10	6/20 (30)	13/18 (72)
AAORCA	20/49 (41)	1/20 (5)	16/19 (84)	20/20 (100)	18/20 (90)	8.5 (7-10)	4	9/18 (50)	12/14 (86)
Both	1/49 (2)	0	1/1 (100)	1/1 (100)	1/1 (100)	4	0	1/1 (100)	1/1 (100)
Total	49/49 (100)	5/49 (10)	40/45 (89)	48/49 (98)	43/49 (88)	8 (5-10)	14	16/39 (41)	26/33 (79)
A. vs B. P values for patients without ischemia vs patients with ischemia									
AAOLCA	<.0001	.06	.0004	.13	.007	.5		.04	.02
AAORCA	<.0001	.2	.002	1	1	.04		.5	.7
Total	–	.002	<.0001	.32	.14	.3		.4	.2
C. Nonsudden cardiac event patients (n = 31)									
AAOLCA	16/31 (52)	1/16 (6)	13/15 (87)	15/16 (94)	14/16 (88)	7 (4-10)	4	5/13 (38)	7/12 (58)
AAORCA	14/31 (45)	0	11/14 (79)	14/14 (100)	13/14 (93)	9 (8-10)	4	6/12 (50)	7/9 (78)
Both	1/31 (3)	0	1/1 (100)	1/1 (100)	1/1 (100)	4	0	1/1 (100)	1/1 (100)
Total	31/31 (100)	1/31 (3)	25/30 (83)	30/31 (97)	28/31 (90)	8 (5.5-10)	8	12/26 (46)	15/22 (68)
D. Sudden cardiac event patients (n = 18)									
AAOLCA	12/18 (67)	3/12 (25)	10/10 (100)	12/12 (100)	10/12 (83)	5 (2.8-8.5)	6	1/7 (14)	6/6 (100)
AAORCA	6/18 (33)	1/6 (17)	5/5 (100)	6/6 (100)	5/6 (83)	8 (7-10)	0	3/6 (50)	5/5 (100)
Total	18/18 (100)	4/18 (22)	15/15 (100)	18/18 (100)	15/18 (83)	7 (3-10)	6	4/13 (31)	11/11 (100)
C. vs D. P values for nonsudden cardiac event patients vs sudden cardiac event patients									
AAOLCA	.4	.3	.5	1	1	.5		.4	.1
AAORCA	.4	.3	.5	–	.5	.6		1	.5
Total	–	.05	.15	1	.7	.5		.5	.07

Missing values not shown can be derived by comparing the denominator with the number of patients in the Total column. Both denotes patients with AAOLCA and AAORCA. High orifice denotes those at or above the sinotubular junction. In the surgical column, patients who died and were not eligible for surgery were removed from the denominator. IQR, Interquartile range; M, missing; AAOLCA, anomalous aortic origin of a left coronary artery; AAORCA, anomalous aortic origin of a right coronary artery; LAD, left anterior descending.

left anterior descending or isolated anomalous circumflex underwent an operation.

Although 236/262 (90%) patients who underwent provocative testing were found to not have ischemia, nearly half (109/236; 46%) still underwent an operation (23 AAOLCA, 85 AAORCA, 1 with both). Additionally, 187 patients underwent an operation without provocative testing (54 AAOLCA, 130 AAORCA, 3 with both). Finally, 132 patients did not have an operation, but

had provocative testing, of which 5 were positive (2 AAOLCA, 3 AAORCA, all alive), and 127 were negative. The 2 AAOLCA patients are further described in the following section.

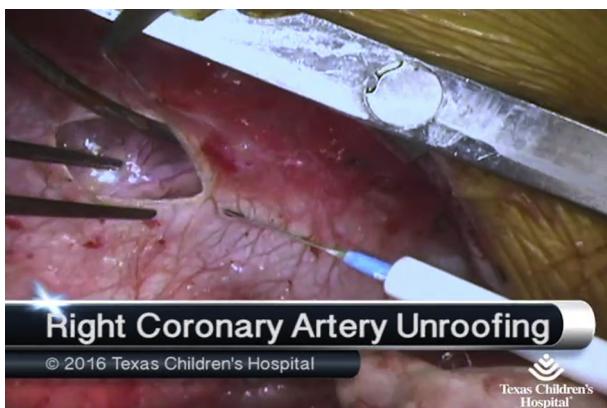
Surgical Patients With Evidence of Ischemia

Among patients with ischemia, 40 underwent an operation (23/45 [51%] AAOLCA, 16/45 [36%] AAORCA, and 1/45 [2%] patient with both). Patients who died before an

operation were removed from the denominator, leaving 45 patients. Primary surgical procedures included unroofing (n = 35), patch ostioplasty (n = 4), and reimplantation (n = 3). For a demonstration of unroofing, please see [Video 1](#). Reoperation occurred in 4/40 (10%) patients to address ostial stenosis (3 AAOLCA [2 had postoperative symptoms and subsequent investigations, and 1 suffered a postoperative cardiac arrest]; and 1 AAORCA [reoperated on postoperative day 1 for arrhythmia]). See [Table 5](#), section A for a listing of the primary procedures that patients with ischemia underwent, and [Table 5](#), section B for a description of the reoperations that patients underwent. See [Appendix E3](#) for a detailed description of the 9 patients with ischemia who did not undergo surgery (5 AAOLCA and 4 AAORCA).

DISCUSSION

Until recently, descriptions of AAOCA variants have been primarily limited to case reports, autopsy series, and single-institution series.^{1,9-11,22-28} These reports have suggested that high-risk anatomy primarily includes AAOLCA, especially in those with an interarterial course, and that interarterial AAOLCA is less common than interarterial AAORCA, although it carries a greater risk of sudden cardiac events.^{22-24,29,30} However, because of the rarity of diagnosed AAOCA and the low frequency of presentation with sudden cardiac events, evaluating the risk of ischemia and sudden cardiac events, and the features associated with each, in addition to surgical management, has proven difficult. Our cohort is unique in that it is a multi-institutional representation of children and young adults with and without ischemia in the general population, who might or might not be involved in sports and other physical activities.^{1,11,24-26}



VIDEO 1. Unroofing of anomalous aortic origin of a right coronary artery in a patient with an intramural course. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30701-9/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30701-9/fulltext).

Race

When examining demographic characteristics, race did seem to play a role because there was a higher proportion of African American patients within patients with ischemia versus patients without ischemia, compared with other races. Because this is, to our knowledge, the first time this association has been noted with AAOCA, further assessment is necessary in a population in which race is more completely captured. However, this might indicate a population that is at higher risk for ischemia, and who require more careful assessment and consideration for intervention.

Age of Patients With Ischemia and Sudden Cardiac Events

One possible explanation for why patients with ischemia were found to have a median age significantly older than those without ischemia is because older children are more likely to experience ischemia because of increasing intensity of exertion, sports practices, and competition compared with younger children. However, there was 1 sudden cardiac event that occurred as young as 6 years of age (interarterial, intramural AAOLCA). Although rare, it does suggest that an operation might be considered in select cases at a younger age in those with an interarterial and/or intramural AAOLCA course. This is younger than the previously suggested age of approximately 10 years, after which children are believed to be at higher risk of adequately exerting themselves and inducing an event.¹⁴ However, a patient's larger size when older might also make it safer to surgically address the coronary arteries, which will also be larger.

Ischemia Testing

Interestingly, in our cohort, there was a large number of patients who had not undergone provocative testing (n = 275). This was the youngest group of patients with a median age of 9.0 years (interquartile range, 2.5-14.0). We believe that the lack of testing can be partially explained by the young age of this group, because likely some proportion were believed to be too young to undergo provocative testing. However, there were others, as evidenced by the upper end of the interquartile range, who were old enough to undergo some sort of provocative testing and did not. There were 127/210 (60%) unclassified AAORCA patients who underwent surgical repair without any provocative testing, having had only anatomic imaging with echocardiography and/or axial imaging. This was not in keeping with what we would have expected because the current guidelines recommend provocative ischemia testing for AAORCA patients upon diagnosis to help in risk stratification.¹⁴ Provocative ischemia testing is likely a highly valuable source of information for baseline assessment, and for subsequent evaluation after an operation.

TABLE 5. Primary procedures in surgical patients with ischemia

Procedure 1 N = 40, M = 0	Procedure 2 N = 4, M = 0
Unroofing = 3 (8%) AAOLCA with CM	Bypass graft = 1 (25%) AAORCA
Unroofing with tacking = 25 (63%) (13 AAOLCA [9 CM], 11 AAORCA [3 CM], 1 both)	Patch ostioplasty = 2 (50%) AAOLCA (1 CM)
Unroofing, PA translocation = 1 (3%) AAORCA	Ostioplasty = 1 (25%) AAOLCA
Unroofing with tacking, PA translocation = 2 (5%) (1 AAOLCA, 1 AAORCA)	
Ostioplasty = 1 (3%) AAORCA with CM	
Patch ostioplasty = 2 (5%) AAOLCA (1 CM)	
Neo-ostial window creation with tacking = 1 (3%) AAOLCA	
Reimplantation = 1 (3%) AAOLCA	
Unroofing, aortocoronary window = 1 (3%) AAOLCA	
Unroofing, patch ostioplasty = 1 (3%) AAORCA	
Unroofing, reimplantation = 1 (3%) AAORCA with CM	
Unroofing with tacking, patch ostioplasty, reimplantation = 1 (3%) AAOLCA with CM	

Adjunct procedures might include commissural takedown ± resuspension. M, Missing; AAORCA, anomalous aortic origin of a right coronary artery; AAOLCA, anomalous aortic origin of a left coronary artery; CM, commissural manipulation; PA, pulmonary artery.

Anatomical Features Associated With Evidence of Ischemia and Sudden Cardiac Events

This study showed, to our knowledge for the first time, that patients with ischemia were more likely to have AAOLCA versus AAORCA. No particular coronary artery was more likely in those with sudden cardiac events versus without sudden cardiac events. As well, twice the number of patients with sudden cardiac events had AAOLCA versus AAORCA, showing again that patients with AAOLCA are at higher risk for ischemia. However, in a comparison of the proportion of nonsudden cardiac event patients who had AAOLCA versus sudden cardiac event patients who

had AAOLCA, no difference could be shown. Similarly, no difference could be found for AAORCA patients. Although the association of ischemia with AAOLCA has been suggested by previous studies, in this study we attempted to capture all patients with AAOCA, instead of specific subpopulations, to show these proportions and their significance.^{22,29} In addition, we showed that AAORCA is not always a benign lesion. In patients with ischemia, the proportion of AAOLCA to AAORCA was 1.4:1, and in those with sudden events, AAOLCA to AAORCA was 2:1.

We also identified several anatomic features that were associated with increased risk of ischemia: (1) an intramural

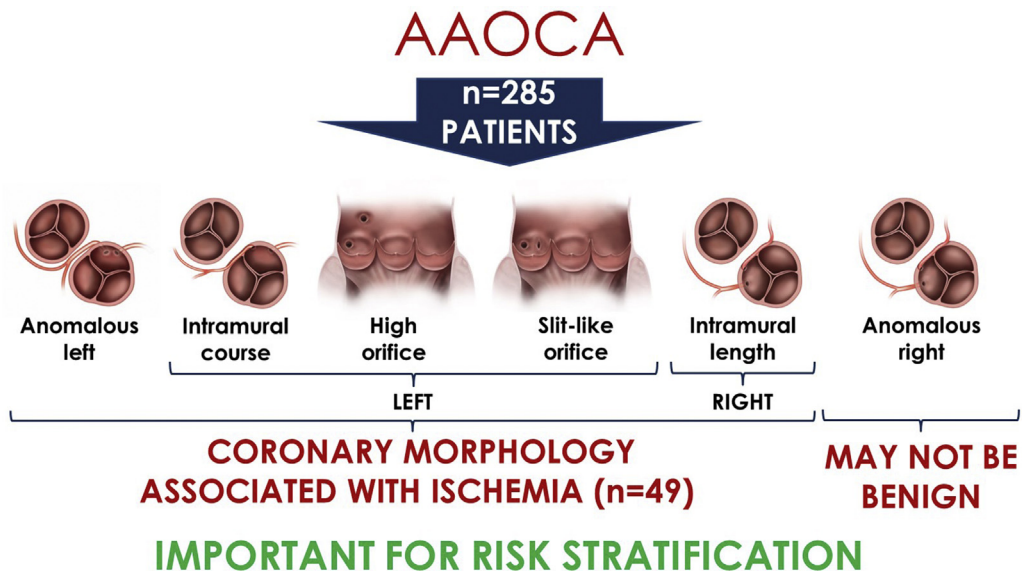


FIGURE 2. Primary findings related to myocardial ischemia in anomalous aortic origin of a coronary artery (AAOCA).

course, a high take-off from the aorta, and/or a slit-like orifice in AAOLCA, and (2) a longer intramural course in AAORCA. Of the 18 patients who had a sudden cardiac event, all had AAOCA with a slit-like orifice and an interarterial coronary artery course, and all but 3 were intramural. We were perhaps unable to determine anatomic characteristics that were associated with patients who had sudden cardiac events because of their limited number in this study.

These results suggest that it is not the interarterial aspect per se, but the intramural course, increased intramural length, and a high and/or slit-like orifice that appear to contribute most to risk for ischemia. These details, which usually cannot be gleaned from echocardiographic imaging, are best determined using computed tomographic angiography or magnetic resonance imaging.^{4,30-32} Future studies should evaluate these characteristics in more detail. These features should be considered in risk assessments and potentially in future AAOCA expert guidelines, which currently recommend operation only for interarterial AAOLCA and for symptomatic patients.^{14,33}

Surgical Management

Nearly all of the patients with ischemia who underwent operation had an unroofing procedure, similar to our previous report.¹⁸ Of these patients, 10% required reoperation to address ostial stenosis at various times. This finding, together with previous evidence for persistent ischemia after repair, suggests that techniques such as perioperative angiography (completion angiography) should be considered, and postoperative follow-up, including advanced imaging and perhaps provocative testing, are important.³

Limitations

In addition to surgical patients, we enrolled nonsurgical and SCD patients in our cohort. We are primarily dependent on participating cardiologists at each site (not traditionally involved with the CHSS) to find these patients. As such, we do not know if we captured all patients at a given site, in addition to patients who never presented for care. It is also unknown whether patients treated at CHSS institutions are different, and potentially more complex, than those managed at nonparticipating sites. This might result in an inflation in the proportion of ischemic and surgical patients in our cohort. We also only included patients in our study who were diagnosed at less than or equal to 30 years. This age was selected to capture patients at highest risk of an ischemic event and because CHSS institutions generally treat pediatric and young adult patients; we would have missed a large proportion of older patients.¹⁵ Workup of patients was also variable, as evidenced by those without any provocative testing and the limited use of advanced techniques. As such, we did not include unclassified patients in our nonischemic group because we wanted the

comparison group to be truly ischemia-negative, although we appreciate that this might introduce bias. Finally, our data accuracy is based on the accuracy of information sent from the participating member institutions. This is important because coronary artery anatomy was determined from institutional imaging reports rather than from expert review of images.

Summary

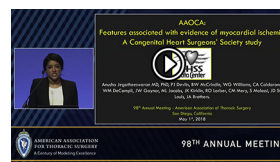
Within our large cohort of AAOCA patients, less than or equal to 30 years, we found that ischemia is more likely with AAOLCA, presence of an intramural course, a longer intramural course, and a high or slit-like orifice. However, no anatomic features distinguished those who presented with sudden cardiac events. We also established that AAORCA might not always be benign. AAORCA was present in just under half of patients with ischemia and one-third of those with sudden cardiac events. See [Figure 2](#) for a graphical representation of these take-home messages. Notably, there was no statistically significant difference in the proportion of AAOLCA or AAORCA in patients with sudden cardiac events. Almost all ischemic patients underwent unroofing (most with tacking) as a primary procedure.

CONCLUSIONS

Our findings of associations between morphologic features and ischemia, and that AAORCA might not always be benign might provide a basis for improved risk stratification and refinements to standardized guidelines, including delineation of those at risk for ischemia and recommendations for surgery. Finally, there remains a strong need for the standardized workup of AAOCA patients and reporting of morphologic features, which will allow much needed easy aggregation and reporting of outcomes for these patients.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18May01/20ABC%201.Plenary/S79_4.mp4.



Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: anomalous aortic origin of a coronary artery, congenital heart disease, database, epidemiology, ischemia

Discussion



Dr Charles D. Fraser (Houston, Tex).

I would really like to thank the Association for the privilege of discussing this important presentation. Dr Jegatheeswaran has done her usual masterful job of presenting important information for us to consider in this vexing topic of anomalous aortic origin of the coronary artery, or AAOCA. I have also had the advantage of reading the manuscript, and I know that time limited some of the data that Dr Jegatheeswaran could present, so I will embellish a little bit on that.

She and colleagues have analyzed data from the Congenital Heart Surgeons Society AAOCA registry, which is a critically important prospective registry now of over 560 patients. To re-emphasize, AAOCA may or may not be associated with demonstrable myocardial ischemia or sudden cardiac death. The majority of patients are actually incidentally discovered to have this lesion, and that's recently more frequently associated with mass screening programs, which are controversial.

Even in the absence of ischemia or symptoms, the diagnosis is problematic: it's confusing for practitioners; it's frightening for patients and families who may be essentially disabled by the diagnosis; there's uncertainty regarding surgery and approach, activity limitations, and long-term surveillance.

Recent guidelines, which I participated in creating, have recommended surgery for patients with an interarterial anomalous left coronary artery or patients with either anomalous left or right coronary arteries and evidence of ischemia. Dr Jegatheeswaran's data bring many new important revelations. Among these, the proportion of African Americans with ischemia was significantly higher than other races. Anomalous right coronary artery is less likely to have ischemia but it's not totally benign. Despite the guidelines, a very large percentage of patients with anomalous right coronary arteries do undergo surgery. A longer documented intramural course increases the risk of ischemia. Almost 50% of patients without provocative evidence of ischemia do actually undergo surgery.

Very concerning, among the 40 patients with ischemia who underwent surgery, 10% required an ostial revision or had a problematic operation. And then finally, the specific anatomic features associated with ischemia include an intramural course, a high take-off, a slit-like ostium for anomalous left, and a longer intramural course of anomalous right.

So I have many questions I could ask. I will start with, given the findings of the specific anatomic features associated with increased risk, particularly the length of intramurality, what is your recommended diagnostic assessment methodology?



Dr Anusha Jegatheeswaran (Toronto, Ontario, Canada). Thanks for your question, Dr Fraser. Many people want to know what method should be used, and I think that's a complex question, because different centers have had good results using different methodologies. I think it is important that we acknowledge those results and that I also mention this study was not designed to answer that question.

In addition, people often want to know, what the length of the intramural segment is. There has not been great correlation between advanced imaging and intraoperative

findings as we know. We are yet to figure out which modality is able to capture this best. The first step to figure this out is standardized reporting. I will make a plea to all of you to help us get that data by following a standard approach. Despite the fact that intraoperatively at Texas Children's Hospital, a unique technique is used to measure the length of the intramural segment by using a suture, that's not the data that clinicians have preoperatively to make their decisions. So, although it's great to get that exact measurement, that's never what a physician has when they are making their clinical assessment. We have yet to figure out which method will allow us to best figure it out preoperatively, even if it means using whatever technique is done best at your institution. However, hopefully we will move toward a standard way of figuring that out and all centers will be able to adopt that technique for use preoperatively, intraoperatively, and also postoperatively.

Dr Fraser. Completely agree.

Given these findings, which are, again, very important, should the guidelines be revisited and in some way revised, and if so, how?

Dr Jegatheeswaran. Currently the guidelines are really just expert consensus documents. However, it includes some of the best data that we have right now. Similarly, what we just presented could be included among these data. We had 550 patients with detailed abstraction of their reports. These data were not core lab-reviewed. One of our next steps is to review every preoperative image in the core lab, and then further determine which morphologic variants are associated with increased risk.

The current consensus guidelines were primarily developed from military autopsy series and the data of competitive athletes who died suddenly. Our data do have something important to add to that, but it is by no means the final answer.

Dr Fraser. Okay, thank you. I have to ask, what are your thoughts on mass screening programs? Is this an advisable thing, going into large school districts, screening all high school age students?

Dr Jegatheeswaran. So that's a really contentious issue, as we all know—

Dr Fraser. That's why I asked.

Dr Jegatheeswaran. —and I don't think we have the right answer. It's a paradox. Likely we will screen everybody, find some patients who have benign lesions and then inadvertently operate on them, despite the surgical risks. However, we truly don't have the answers as to what to do with those patients yet. Even performing ECGs in athletes is contentious, and although Europe has adopted that, the United States has yet to do so. Mass screening is an order of magnitude more invasive.

I think the problem is that what we really need is the long-term follow-up of this large multi-institutional cohort.

There are so many variations... in fact, there are an exponential number of variations, and we haven't yet figured out what to do with each variant. So, we need long-term follow-up, and of course we must consider the cost versus benefit of screening. I think when we know something more definitive, such as how to risk-stratify patients, we can consider moving toward mass screening to identify morphologic variants or likely high-risk combination of features that are currently unknown. However, we are not there yet.



Dr Hanij Najm (Cleveland, Ohio). I want to congratulate you on this important study and collection of a very large number of those patients, which, I agree with you, we have a lot of unanswered questions.

You have indicated in your presentation the number of patients who have had ischemia in the left and right anomalies as well as patients who had cardiac events in the left and right anomalies. Have you correlated those patients who had cardiac events with those patients who have had cardiac ischemia? Because what we found was that not infrequently, and I am sure surgeons around the room would agree, you establish ischemia before surgery, you do the surgery and you still have some ischemia postop. And it depends on what kind of ischemia study you have done and how elaborate that is; there is always a false positive and/or a false negative in all these studies. So I agree that there are still a lot of unanswered questions. We started doing PET scans to look at ischemia and FFRs, utilizing our adult colleagues experience, to tell us whether these are significant or not.

So going forward, first of all, if you could address the correlation between the presence or absence of ischemia and the cardiac events, and do our surgeries fix the ischemia, and what is the best modality of detecting ischemia? Is it the FFR, is it functional or anatomical measures that would be best for those patients?

Dr Jegatheeswaran. With regard to correlation, the sudden cardiac event patients in our study were a subset of the ischemia patients. There were 49 ischemia patients, 18 of whom had sudden cardiac events. We couldn't find any anatomic features associated with patients who had sudden cardiac events. Part of that is probably because we only had 18 patients, so it was a really small subgroup in which to look for features. What we need is a larger cohort of patients, and we are still enrolling in order to figure out that answer.

In terms of postoperative ischemia versus preoperative ischemia, we don't have that data in our study, so we are unable to answer that. We are still doing follow-up on these patients, and for a lot of the patients we don't yet have their postoperative evaluations.

And with regard to your last question, I don't know what the answer is with respect to the best method. We know for provocative testing sometimes it's positive, sometimes it's negative, and different circumstances may cause you to have ischemia in some instances versus others. So currently, we don't have a gold standard method. Of course, it would be nice to do something that is not invasive, as opposed to FFR.

Dr Fraser. So I have to end with one hard question. You are now the world's expert on this subject. All the patients that have been enrolled in the study consented. I know from our experience that they are expecting some follow-up. So I will bet that what's going to happen is you are going to get called by a family, and the question is going to go like this:

I have a 14-year-old daughter who is a soccer player and I'm really worried that she might have a problem. She is asymptomatic. She has gotten an echo and she has got an anomalous right coronary artery from the left sinus, it goes right behind the pillar, and it looks to have about a 6- to 7-mm intramural segment. Asymptomatic, provocative testing is negative.

Dr Jegatheeswaran. That's a great question and this is the conundrum that we face, which is why we are doing this study and why you are asking me this question. This study really wasn't designed for individual patient prediction. Right now we don't have the answer, partially because we don't have long-term follow-up.

Of course, what we did find in our study is that there is a risk for surgery. We had 4 patients who had reoperations for ostial stenosis. So, we don't want to give patients the false hope that surgery is going to solve everything. Of course, it's a small number; we need more patients and long-term follow-up to get a clearer picture of the risks.

Because patients have numerous subtleties and combinations of features, in order to accrue any kind of meaningful data we need more patients, more data, and then one day hopefully we will be able to develop a calculator for prediction of who should undergo what type of surgery or management on the basis of their anatomical features. That's really our ultimate goal.

Dr Fraser. I think your data suggest most of those patients are getting an operation.

Dr Jegatheeswaran. The data definitely do suggest that. We had 236 patients who had negative ischemia testing. Of course, we know negative ischemia testing doesn't actually mean they are negative, but 46% of those patients despite negative ischemia testing underwent surgery.

In many cases, I'm sure that the surgeons are forced to operate. However, the caveat is that we don't know what the right answer is yet.

Dr Fraser. Very well done. Thank you.

APPENDIX E1. MEMBER INSTITUTIONS

Johns Hopkins All Children's Hospital, Tampa, Florida
 Arnold Palmer Hospital for Children, Orlando, Florida
 Cleveland Clinic Foundation, Cleveland, Ohio
 Cardinal Glennon Children's Hospital, St. Louis, Missouri
 Boston Children's Hospital, Boston, Massachusetts
 Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois
 Children's Hospital of Michigan, Detroit, Michigan
 Children's Minnesota, Minnesota, Minneapolis
 Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
 Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
 Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
 Rudy Children's Hospital, San Diego, California
 Seattle Children's Hospital, Seattle, Washington
 Children's Hospital of Wisconsin, Milwaukee, Wisconsin
 Children's Mercy, Kansas City, Missouri
 Children's National, Washington, District of Columbia
 Cedars-Sinai Medical Center, Los Angeles, California
 Nemours/Alfred I. Dupont Hospital for Children, Wilmington, Delaware
 Children's Healthcare of Atlanta, Atlanta, Georgia
 Inova Children's Hospital. Fall's Church, Virginia
 The Hospital for Sick Children, Toronto, Ontario
 Johns Hopkins Children's Center, Baltimore, Maryland
 Levine Children's Hospital, Charlotte, North Carolina
 Loma Linda University Children's Hospital, Loma Linda, California
 Nicklaus Children's Hospital, Miami, Florida
 C.S. Mott Children's Hospital, Ann Arbor, Michigan
 Mayo Clinic Children's Center, Rochester, Minnesota
 Children's Hospital at Montefiore, Bronx, New York
 Kravis Children's Hospital at Mount Sinai, New York, New York
 MUSC Children's Hospital, Charleston, South Carolina
 Hassenfeld Children's Hospital, New York, New York
 Primary Children's Hospital, Salt Lake City, Utah
 St. Louis Children's Hospital, St. Louis, Missouri
 Lucile Packard Children's Hospital, Palo Alto, California
 Texas Children's Hospital, Houston, Texas
 Tulane Hospital for Children, New Orleans, Louisiana
 Stollery Children's Hospital, Edmonton, Alberta
 University of Texas Southwestern Medical Center, Dallas, Texas
 Masonic Children's Hospital, Minnesota, Minneapolis
 Yale New Haven Children's Hospital, New Haven, Connecticut

APPENDIX E2. INCLUSION AND EXCLUSION CRITERIA, DATA COLLECTION, DATA AGGREGATION OF ANATOMICAL FEATURES, AND DETAILED STATISTICAL METHODS**Inclusion and Exclusion Criteria**

Inclusion criteria for the registry are a diagnosis of AAOCA at less than or equal to 30 years, with a structurally normal heart or a hemodynamically insignificant concomitant cardiac lesion (eg, patent ductus arteriosus, atrial septal defect, restrictive ventricular septal defect, mild pulmonary valve stenosis, or bicuspid aortic valve without stenosis) not requiring surgical or catheter-based intervention. Exclusion criteria are coronary artery ostial atresia, coronary artery aneurysm, myocardial bridging, coronary-cameral fistula, anomalous aortic origin of a coronary artery from the pulmonary artery, and any concomitant hemodynamically significant structural heart lesion.

Data Collection

Patient data were abstracted from copies of institutional medical records submitted to the CHSS Data Center, for initial and subsequent assessments, hospitalizations, and procedures, and entered into a database by CHSS Data Center staff. These variables have been defined and described in our previous work and include patient demographic characteristics, presentation, and symptoms from clinic notes, operative details from reports, and anatomical details from imaging reports, operative records, and autopsy reports.² Coronary artery anatomy was depicted as individual morphologic components for classification and analysis as shown in the standardized atomization form given to participating centers, as previously described ([Online Data Supplement](#)). Anatomical components collected included which coronary artery is anomalous, the morphology of the origin (2 orifices, common orifice, single orifice with common trunk, slit-like orifice, high take-off, acute angulation), and the course of the coronary artery.

The anatomical features collected for each patient were based on data obtained from preoperative echocardiogram, computed tomography, and/or magnetic resonance imaging reports. In addition, surgical atomization reports completed by the surgeon were used, if the patient underwent an operation. If these were not provided, a report was completed by Data Center staff using the operative report. In several cases, the only anatomical description available was from an autopsy report (n = 4). We have also previously described our method for using multiple patient reports to obtain missing data or clarify contradictory data for the same patient.

Data Aggregation of Anatomical Features

Aggregated composite morphology for each patient was based on available diagnostic studies, and surgical data.

Similar to the technique used in our previous report, only preoperative diagnostic studies were used, before any surgical procedures. These were concatenated to reflect the global morphology of each patient using an algorithm that first retained all values that were similar among all sources (echocardiograms, computed tomography, magnetic resonance imaging, operative notes, and surgeon-completed data forms), then the variables that were only available from one source were added. Finally, if a variable had differing values, these were adjudicated by Data Center staff. The gold standard was considered to be a data form that was completed by the surgeon on the basis of his/her intraoperative findings, followed by operative notes, magnetic resonance imaging or computed tomography, and finally echocardiography.

Statistical Methods

Categorical variables were summarized using frequencies and percentages. The normality of all continuous variables was first evaluated with the Shapiro-Wilk test. Continuous variables were then summarized as medians and interquartile ranges (if non-normal) or, if normally distributed, means and standard deviations. The χ^2 and Fisher exact tests were used to evaluate differences between

groups for categorical variables, whereas the Wilcoxon signed rank test was used to evaluate differences between groups for non-normal continuous variables, and the Student *t* test for normal continuous variables.

APPENDIX E3. DETAILED DESCRIPTION OF 9 PATIENTS WITH ISCHEMIA WHO DID NOT UNDERGO SURGERY.

Nine patients with ischemia did not undergo an operation; 5 had anomalous aortic origin of a left coronary artery (AAOLCA); 1 sudden cardiac death, 1 with sudden cardiac arrest (SCA) died, 1 had SCA while being admitted after presentation with symptoms/elevated biomarkers/abnormal electrocardiogram and died, 2 declined an operation, and 4 had anomalous aortic origin of a right coronary artery (1 with SCA died, 1 lacked follow-up, 2 were referred for an operation). The 2 AAOLCA patients who were alive and had not had an operation both presented with abnormal perfusion scans. One was reluctant to undergo an operation and wanted a second opinion (interarterial AAOLCA with an intramyocardial left anterior descending artery), and the other patient refused to undergo an operation (interarterial intramural AAOLCA with a high ostial take-off at the level of the sinotubular junction).

TABLE E1. Comparison of patients without ischemia versus unclassified patients

Anomalous coronary artery	Total	Dead	Surgery	Interarterial	Intramural	Intramural length, mm	High orifice	Slit-like orifice	
	N (%)	n (%)	n (%)	n (%)	n (%)	Median (IQR) M	n (%)	n (%)	
Patients without ischemia (n = 236)									
AAOLCA	46/236 (19)	1/46 (2)	23/46 (50)	34/41 (83)	18/35 (51)	7.5 (4.5-10)	5	2/32 (6)	10/28 (36)
AAORCA	184/236 (78)	1/184 (1)	85/184 (46)	158/161 (98)	114/131 (87)	6 (4.8-9)	38	44/105 (42)	62/81 (77)
LAD	3/236 (1)	0	0	0	0	0	0	0	0
Circumflex	2/236 (1)	0	0	1/2 (50)	0	0	0	0	0
Both (AAOLCA and AAORCA)	1/236 (0.4)	0	(1/1) 100	0	1/1 (100)	1.5	0	1/1 (100)	1/1 (100)
Total	236/236 (100)	2/236 (1)	109/236 (46)	193/208 (93)	133/170 (78)	6 (4.5-9)	43	47/140 (34)	73/111 (66)
Unclassified patients (n = 275)									
AAOLCA	54/275 (20)	2/54 (4)	38/54 (70)	39/43 (91)	34/42 (81)	5.8 (5-9)	12	10/31 (32)	24/36 (67)
AAORCA	213/275 (77)	4/213 (2)	127/210 (60)	180/182 (99)	125/149 (84)	7 (5-10)	33	38/131 (29)	77/110 (70)
LAD	2/275 (1)	0	0	1/2 (50)	0, 2 M	–	0	0, 2 M	0, 2 M
Both (AAOLCA and AAORCA)	6/275 (2)	0	3/6 (50)	6/6 (100)	2/6 (33)	2.3 (1-3.5)	0	5/6 (83)	0/4 (100)
Total	275/275 (100)	6/275 (2)	168/272 (62)	226/233 (97)	161/197 (82)	7 (5-10)	45	53/168 (32)	101/150 (67)
<i>P</i> values for patients without ischemia vs unclassified patients									
AAOLCA	1.0	1.0	.04	.3	.006	.5	.01	.01	
AAORCA	.9	.4	.005	.7	.5	.3	.04	.3	
Total	–	.3	.0004	.04	.4	.6	.7	.8	

There were 6 patients who died within the unclassified patient group, of whom 2 AAOLCA patients died in the immediate postoperative period, and 4 died from noncardiac causes. We found that 5 centers contributed 10 to 25 patients each to the patients who underwent surgery among the unclassified patients, suggesting these centers had a strategy of operating on anomalous aortic origin of a coronary artery without provocative testing. This is compared with 3 entirely different centers, which contributed 10 to 18 patients each to the patients who underwent surgery among the patients without ischemia. This again suggests an alternate strategy of provocative testing before surgery. Missing values not shown can be derived by comparing the denominator with the number of patients in the Total column. High orifice denotes those at or above the sinotubular junction. In the Surgery column, patients who died and were not eligible for surgery were removed from the denominator. *IQR*, Interquartile range; *M*, missing; *AAOLCA*, anomalous aortic origin of a left coronary artery; *AAORCA*, anomalous aortic origin of a right coronary artery; *LAD*, left anterior descending.

CONG