

Anomalous Coronary Artery Origin and Sudden Cardiac Death

Clinical and Pathological Insights From a National Pathology Registry

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ABSTRACT

OBJECTIVES This study sought to describe the clinical and pathological features of anomalous origin of a coronary artery (AOCA) in sudden cardiac death (SCD) victims.

BACKGROUND AOCA from the inappropriate sinus of Valsalva or from the pulmonary artery is increasingly diagnosed with current imaging techniques. AOCA is a possible cause of SCD.

METHODS We reviewed a database of 5,100 consecutive cases of SCD referred to our specialist cardiac pathology center between January 1994 and March 2017 and identified a subgroup of 30 cases (0.6%) with AOCA. All cases underwent detailed post-mortem evaluation including histological analysis by an expert cardiac pathologist. Clinical information was obtained from referring coroners.

RESULTS The mean age was 28 ± 16 years and 23 individuals were male (77%). In 8 cases (27%), SCD occurred before 18 years of age. Cardiac symptoms were present in 11 individuals (37%), and syncope was the most common ($n = 6$, 20%). Anomalous left coronary artery arising from the right sinus of Valsalva (ALCA) with interarterial course ($n = 11$) and anomalous right coronary artery arising from the left sinus of Valsalva (ARCA) with interarterial course ($n = 11$) were the most common found. ALCA arising from pulmonary artery was present in 7 cases, whereas in 1 case, the left coronary artery arose from the noncoronary cusp. Left ventricular fibrosis was reported in 11 cases (37%) and was mainly sub-endocardial. There was evidence of acute infarction in 2 cases. Death occurred during exercise or emotional stress in 15 (50%) cases. The AOCA variant where death occurred more frequently during physical activity was ALCA (8 of 11, 73%), followed by ALCA arising from pulmonary artery (4 of 7, 57%) and ARCA (2 of 11, 18%).

CONCLUSIONS AOCA is a rare cause of SCD. ALCA and ARCA with interarterial course are the most common anatomical variants recognized at the post-mortem of SCD victims. ALCA is more commonly associated with death during exercise. Cardiac arrhythmias causing sudden death seem most likely in the cases without overt myocardial damage. (J Am Coll Cardiol EP 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

Sudden cardiac death (SCD) is a tragic event that may occur in apparently healthy individuals (1,2). Whereas atherosclerotic coronary artery disease is most common in older individuals (3), the primary cardiomyopathies and channelopathies are

the predominant causes of SCD in the young (<35 years) (4). Coronary artery anomalies have been reported as the second most frequent cause of SCD in young athletes in the United States, accounting for 12% of deaths (5); a recent study from our

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**ABBREVIATIONS
AND ACRONYMS****AOCA** = anomalous origin of coronary artery**ALCA** = anomalous left coronary artery**ARCA** = anomalous right coronary artery**ALCAPA** = anomalous left coronary artery arising from pulmonary artery**SCD** = sudden cardiac death

group reported coronary anomalies in 5% of cases in athletes who died suddenly (6). Most coronary anomalies are thought to be benign anatomical variants and discovered incidentally during diagnostic imaging or at autopsy. A coronary artery arising from the wrong sinus but not having an interarterial course is also considered benign, especially if there is no evidence of narrowing or myocardial ischemia on imaging (7). The most feared coronary anomalies are those arising from the pulmonary artery or the

wrong sinus with an interarterial course between the pulmonary artery and aorta (Figure 1) (8,9). The interarterial course may also have an intramural segment running within the aortic wall. The most common subtype is the anomalous right coronary artery arising from the left coronary cusp (ARCA), followed by anomalous left coronary artery arising from the right coronary cusp (ALCA). Anomalous left coronary artery from pulmonary artery (ALCAPA) is extremely rare and usually is fatal in early infancy but adult cases can survive with collateral development (10). In a recent screening study using cardiac magnetic resonance imaging in a general population of adolescents, the reported prevalence of anomalous origin of a coronary artery (AOCA) was 0.44% (11).

The aim of the study was to describe the clinical and pathological features of a cohort of SCD victims with AOCA diagnosed at expert autopsy.

METHODS

SETTING. The Cardiac Risk in the Young Center for Cardiac Pathology at St. George's University of London is led by an expert cardiac pathologist (M.N.S.) and receives over 500 whole hearts of cases of SCD across the United Kingdom each year.

STUDY POPULATION. We reviewed a total of 5,100 cases of SCD referred to the Cardiac Risk in the Young center from 1994 to 2017. Thirty cases (0.6%) with AOCA were identified. Demographics, previous cardiac symptoms, circumstances of death, and anatomical features of the coronary artery anomaly were analyzed. Circumstances of death were subdivided broadly into death occurring during exercise or emotional stress and death during rest or sleep.

CLINICAL INFORMATION. Data were collected prospectively and stored on an electronic database and included demographics, past medical history, family history, cardiac symptoms, the nature and level of physical activity, and exact circumstances of death. These were derived from coroners' officers' reports,

pathologist reports, interviews with the family of the deceased, potential witnesses of the SCD, and reports from the deceased's family physician.

POSTMORTEM EXAMINATION. An initial full post-mortem evaluation of the body was carried out by the referring pathologist for each case. A toxicology screen was conducted in all cases in accordance with the usual investigation of sudden and unexpected deaths in the United Kingdom. After excluding other extracardiac causes of death, the whole heart was referred for expert examination. For each whole heart, the weight was recorded in grams and comprehensive macroscopic examination and histopathological analysis performed in accordance with national and international guidelines (12). A minimum of 10 blocks of tissue were taken as reported previously and fixed in formalin and embedded in paraffin (13,14). Sections of myocardium were then taken and stained with hematoxylin and eosin as well as elastic Van Gieson stain. To examine the origins of coronary vessels, an incision was performed along the aortic wall and the aortic valve was exposed. The origin of each artery was identified and a probe with a diameter of 2 mm was inserted in the coronary ostia to assess the presence of stenosis. The vessels were then dissected and examined with transverse cuts each 2 mm throughout their whole length (14).

ETHICAL APPROVAL. Ethical and research governance approvals have been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymized research in each case.

STATISTICAL ANALYSIS. Statistical analysis was performed using the PASW software (version 18.0, PASW Inc., Chicago, Illinois). Results are expressed as mean \pm SD for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's *t*-test for continuous variables with correction for unequal variance when necessary and chi-square test or Fisher exact test, as appropriate for categorical variables. Comparisons between continuous variables among groups were performed with analysis of variance—using the Brown-Forsythe statistic when the assumption of equal variances did not hold—while the proportions were compared by means of the chi-square test, using Fisher exact test when necessary.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. Table 1 lists the main clinical and pathological features of the 30 individuals diagnosed with AOCA. The

mean age at death was 28 ± 16 years: SCD occurred before 18 years of age in 8 cases (27%) and over the age of 50 years in 3 cases (10%, diagnosed with ALCA, ARCA, and ALCAPA, respectively; whereas the individual with ARCA had a significant atheromatous plaque in the right coronary artery, the others did not exhibit any significant atheromas). The cohort comprised predominantly male subjects ($n = 23$, 77%).

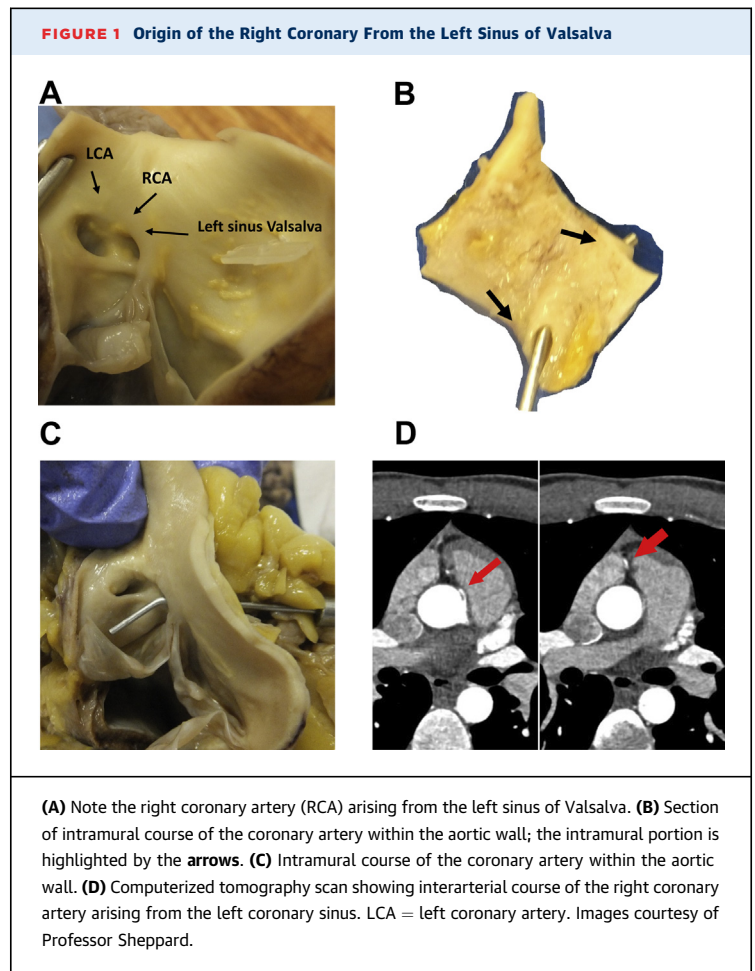
Cardiac symptoms were present in 11 individuals (37%) and syncope was the most common ($n = 6$, 20%), followed by chest pain ($n = 5$, 15%). Two patients (6%) had palpitations, and 1 (3%) reported breathlessness. Most SCD victims did not have any significant past medical history. None had a family history of premature sudden death. Two women were diagnosed prior to death with ALCAPA: one, despite suffering myocardial infarction at birth, led a normal life, with no cardiac symptoms and 2 successful pregnancies; the other had a myocardial infarction and underwent corrective surgery 12 years before her death.

Death occurred during exercise or emotional stress in 15 cases (50%). The remaining 15 individuals (50%) died at rest, including 7 (23%) who died during sleep.

POSTMORTEM CHARACTERISTICS. The mean heart weight was 367 ± 115 g.

Coronary anatomy. The most common anomalies were anomalous right coronary artery with interarterial course ($n = 11$, 37%) and anomalous left coronary artery with interarterial course ($n = 10$, 37%); in 1 individual with ALCA, the course of the coronary artery was retroaortic. An aortic intramural course of the abnormal artery was present in 11 cases (37%) (7 cases with ALCA and 4 cases with ARCA) and its average length was 6 mm. ALCAPA was present in 7 cases (23%); in the remaining case, the left coronary artery arose from the noncoronary cusp near the commissure between the posterior and the left cusps. The ostium was small and the proximal portion of the left coronary artery was horizontal with an initial intramural course. The course of the anomalous coronary was normal without narrowing.

Histopathology. Left ventricular fibrosis was reported in 11 cases (37%) and was mainly sub-endocardial (Table 1). In 2 cases the fibrosis was mainly distributed at the level of the posterior wall (1 ARCA and 1 ALCA); in 1 case the fibrosis was anterolateral; in 1 case it was at the level of the inter-ventricular septum and anterolateral; in 1 case it was at the level of the posterior wall and anterolateral, and in 4 cases it was patchy involving several segments. In the remaining 2 cases there was



evidence of acute infarction (1 ARCA case with distribution at the level of the posterior wall and 1 ALCAPA case with distribution at the level of the posteroseptum), characterized by a combination of interstitial inflammatory infiltrate consisting of a mixture of neutrophils, lymphocytes and histiocytes, and widespread contraction band necrosis. Only 5 of 11 individuals found to exhibit left ventricular fibrosis had previous cardiac symptoms: chest pain ($n = 3$) and syncope ($n = 2$).

DIFFERENCES ACROSS SUBTYPES. The age at death and sex were similar across the different AOCA subtypes although there was a trend toward younger age in the anomalous left coronary artery subgroup (Table 2). Cardiac symptoms were more frequently reported in ALCA (7 of 11, 64%), followed by ALCAPA (3 of 7, 43%) and ARCA (1 of 11, 9%); $p = 0.025$ between ALCA and ARCA (Figure 2A). Death occurred more frequently during physical activity or emotional stress in ALCA (8 of 11, 73%), followed by ALCAPA (4 of 7, 57%) and ARCA (2 of 11, 18%); $p = 0.031$

TABLE 1 Clinical and Histopathological Features of SCD Victims With AOCA

Age, yrs	Sex	Cardiac Symptoms	Circumstances of Death	HW (g)	LV Fibrosis
ALCA					
17	M	—	Died during exertion	320	—
43	M	—	Died at rest	451	—
18	M	—	Died during exertion	316	—
58	F	Palpitations CP	Died during exertion	340	—
15	M	Syncope	Died during exertion	318	—
13	M	Syncope	Died during exertion	220	—
11	M	Syncope	Died in sleep	204	—
15	M	CP, syncope	Died during exertion	341	—
13	M	Syncope	Died during exertion	140	—
28	F	Palpitations	Died in sleep	431	—
16	M	—	Died during exertion	350	Posterior
ARCA					
39	M	—	Died at rest	410	Multiple locations
21	M	CP	Died during exertion	323	Multiple locations
14	M	—	Died in sleep	285	—
43	F	—	Died in sleep	558	—
20	M	—	Died at rest	478	Anterolateral
43	M	—	Died at rest	474	Posterior
23	M	—	Died during emotional stress	337	—
63	M	—	Died at rest	390	Posterior*
38	F	—	Died in sleep	323	—
18	M	—	Died in sleep	390	—
24	M	—	Died at rest	210	—
LCA from noncoronary cusp					
12	M	—	Died during exertion	195	—
ALCAPA					
43	F	—	Died during exertion	648	—
22	F	—	Died at rest	419	Posteroseptum*
27	M	—	Died during exertion	397	—
23	M	CP	Died during exertion	528	IVS and anterolateral
16	M	CP, SOB	Died during exertion	—	Multiple locations
68	F	—	Died in sleep	410	Posterior and anterolateral
33	F	Syncope	Died at rest	428	Multiple locations

*Acute ischemic damage.
ALCA = anomalous left coronary artery; ALCAPA = anomalous left coronary artery arising from pulmonary artery; AOCA = anomalous origin of coronary artery; ARCA = anomalous right coronary artery; CP = chest pain; F = female; HW = heart weight; IVS = interventricular septum; LCA = left coronary artery; LV = left ventricular; M = male; SCD = sudden cardiac death; SOB = shortness of breath.

TABLE 2 Differences Between Subtypes

	ALCA (n = 11)	ARCA (n = 11)	ALCAPA (n = 7)	p Value
Age, yrs	22 ± 15	31 ± 15	33 ± 18	NS
Male	9 (82)	9 (82)	3 (43)	NS
Cardiac symptoms	7 (64)	1 (9)	3 (43)	0.025*
Death during exercise/ES	8 (73)	2 (18)	4 (57)	0.031*
Heart weight, g	309 ± 97	380 ± 91	472 ± 98	0.014†
LV fibrosis	1 (9)	5 (45)	5 (71)	0.03†

Values are mean ± SD or n (%). *Between ALCA and ARCA. †Between ALCA and ALCAPA.
ES = emotional stress; NS = not significant; other abbreviations as in Table 1.

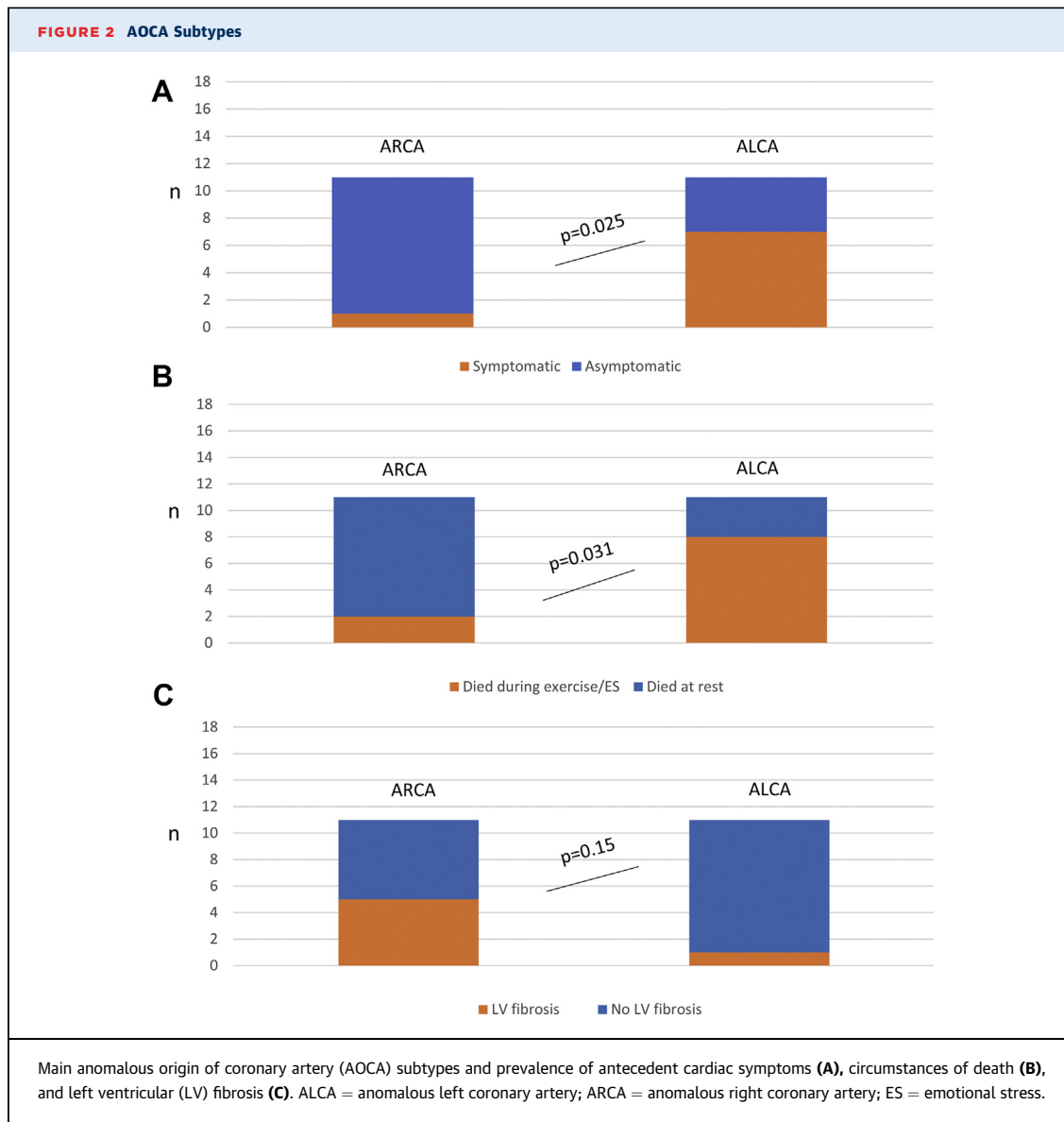
between ALCA and ARCA (Figure 2B). The young individual where the left coronary artery was found to arise from the noncoronary cusp died during exercise. The heart weight was significantly higher in ALCAPA (472 ± 98 g compared with 380 ± 91 g in ARCA and 309 ± 97 g in ALCA, $p = 0.014$ between ALCAPA and ARCA). The prevalence of myocardial fibrosis was also greater in ALCAPA (71%) compared with ALCA (9%, $p = 0.03$) although ARCA also showed a trend toward greater fibrosis (45%) (Figure 2C).

DISCUSSION

This study reports on a cohort of 30 SCD victims where the postmortem identified an anomalous origin of a coronary artery. Anomalous left or right coronary artery arising from the wrong sinus of Valsalva with interarterial course was the most common anatomical variant followed by anomalous coronary artery arising from the pulmonary artery. In ALCA, death occurred commonly during exercise, whereas in ARCA, death occurred usually during rest or sleep.

SCD IN AOCA. Coronary artery anomalies are a relatively rare cause of SCD (15,16). In our study based on postmortem examination of SCD victims, the prevalence of AOCA was 0.6%. Although AOCA is believed to be a cause of death mainly in young individuals, interestingly our series included also cases in the fifth and sixth decades of life. AOCAs are rarely identified during life, especially in asymptomatic individuals (7,17) and the prevalence of interarterial ALCA and ARCA is rare (0.03% and 0.23%, respectively) (7,18), as is ALCAPA: 1 in every 300,000 live births (19). A recent study of healthy volunteers using cardiac magnetic resonance showed similar frequency (11). In a previous study (9), isolated anomalous origin of coronary arteries was observed at autopsy in 2.2% of cases (approximately one-half of deaths were sudden). Such higher prevalence in comparison with our study may be explained with the different methodologies used as we selected only individuals who experienced SCD. Possibly, in some cases the coronary anomaly was an innocent bystander with no causal relationship with death.

Episodic myocardial ischemia resulting in fatal arrhythmias is the main proposed mechanism leading to SCD (16,20–22) and the course of the artery is considered to be a major determinant of outcome (21). An interarterial course of an anomalous left coronary artery is thought to carry the highest risk of SCD, followed by an interarterial course of an anomalous right coronary artery (7). Compression of the first segment of the coronary vessel between the aorta and



the pulmonary artery in a “scissor-like” fashion (21) may result in ischemia (16,23,24). Other proposed mechanisms include an acute angle takeoff and kinking of the coronary artery as it arises from the aorta, which can result in stretching and/or compression of the vessel combined with the ab extrinseco obstruction of the anomalous coronary artery when the aortic root expands during physical activity (9,16,20,22,25). In our series, the most common anomaly types were ALCA and ARCA with an interarterial course. Myocardial fibrosis was present in more than one third of cases and acute myocardial damage was found only in 2 individuals. Therefore, a significant proportion of individuals suffered from

prior myocardial damage that may have led to the development of an arrhythmic substrate. A major challenge in the risk stratification of these patients lays in the rare identification of ischemia (26), and the negative predictive value of a negative stress test in this setting is still unclear (27). Where there is no myocardial damage detected at the postmortem, probably an ischemia-related arrhythmia is the most likely cause of death.

Interestingly, the heart weight was higher in ALCAPA than in the other coronary anomaly subtypes. A possible explanation is that individuals with ALCAPA exhibited more fibrotic changes, probably reflective of a more significant long-standing

ischemic burden. This has probably resulted in cardiac remodeling and therefore the heart weight was higher than in ALCA and ARCA.

SCD DURING PHYSICAL EXERTION. Maron et al. (5) described a ALCA-ARCA ratio of 4:1 in a cohort of young athletes who died suddenly mainly during exercise. In our series, exercise-induced SCD was associated more frequently with ALCA than ARCA where death occurred often at rest or during sleep. The reason for this difference is unclear as fibrosis was also found in our ARCA cases, suggesting that ischemic damage had occurred. It is possible that in ALCA, SCD was caused by ventricular arrhythmias due to acute ischemia affecting a greater bulk of the ventricular myocardium, with a rapid course of events with insufficient time to cause necrosis and/or myocardial fibrosis. Conversely patients with ARCA were older at death and possibly repetitive episodes of ischemia resulted in myocardial fibrosis, which constituted a vulnerable substrate for fatal arrhythmias. Although in ARCA sudden death occurred less frequently during exercise, our study does not provide any information on the actual risk of exercise-induced fatal arrhythmias in individuals with ARCA and therefore does not affect the recommendation to avoid competitive sport in patients diagnosed with this condition (7). Moreover, it is possible that the AOCA was an innocent bystander in some individuals that died during sleep, where death may have been caused instead by an undiagnosed primary arrhythmias syndrome.

ANTECEDENT SYMPTOMS. Similarly to other studies (11,16), a minority of cases (37%) reported cardiac symptoms such as syncope and chest pain prior to SCD. These were more frequently present in SCD victims diagnosed with ALCA. The causes for higher prevalence of antecedent cardiac symptoms in ALCA than in ARCA are unknown; it may be postulated that individuals with ALCA have suffered for more frequent bouts of ischemia resulting in symptoms, due to anatomical reasons. Although it is possible that a thorough diagnostic workup may have identified the AOCA, cardiac symptoms can, however, be common and nonspecific in young individuals (28), making it challenging to base a suspicion of AOCA only on clinical findings. In addition, the sensitivity of 12-lead electrocardiography for detection of an AOCA is very limited. A major challenge in risk stratification in patients with a diagnosis of AOCA is the infrequent identification of ischemia and the probable low negative predictive value of a stress test (26). In a recent study on 23 athletes (6 with ALCA and

17 with ARCA), diagnosis was made by transthoracic echocardiography in 21, only 3 had an abnormal electrocardiogram, and symptoms were present in 10 (9).

The management and therapeutic approach of asymptomatic patients diagnosed incidentally with AOCA is also problematic and subject to debate, especially in individuals without documented ischemia. All cases of suspected interarterial ALCA or ARCA should be considered for coronary computed tomography or cardiac magnetic resonance imaging to visualize anatomic features. Although considerable debate remains regarding the optimal therapeutic management of these patients, surgical repair and coronary deroofting is generally preferred in patients with an early intramural course (7).

STUDY LIMITATIONS. The Cardiac Risk in the Young Centre for Cardiac Pathology is a specialized tertiary referral center for SCD with local pathologists often referring cases when the findings are ambiguous or no clear cause of death can be identified. This may constitute a potential referral bias. Nevertheless, our center receives a high volume of unexpected SCD referrals (>500 per year) of which most are <35 years old. It is possible that some of the decedents of SCD may have had a primary arrhythmia syndrome that was the cause of sudden death and the coronary anomaly was an innocent bystander. In this context, the lack of electrocardiograms in decedents of SCD is a limitation.

CONCLUSIONS

AOCA is a rare cause of SCD, which occurs especially in young individuals. Often SCD is the first manifestation of the disease. ALCA and ARCA with interarterial course, followed by ALCAPA, are the most common anatomical variants recognized at the post-mortem of SCD victims. Exercise appears to be the trigger of fatal arrhythmias mainly in young individuals with interarterial ALCA, whereas in ARCA most SCD occur during rest or sleep. Individuals with ALCA are more likely to be symptomatic prior to death, but they more rarely show evidence of ischemic injury at autopsy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AOCA with interarterial course is a rare cause of SCD. Left ventricular fibrosis is found in approximately one-third of the decedents, and where there is no myocardial damage detected at the postmortem, an ischemia-related arrhythmia is the most likely cause of death. The trigger of sudden death is not always clear as most individuals diagnosed with right coronary artery arising from the left coronary cusp died at rest or during sleep.

TRANSLATIONAL OUTLOOK: A better understanding of the epidemiological burden of coronary anomalies and of the risk of developing fatal arrhythmias is needed. A myocardial substrate for arrhythmias is identified in a minority of decedents of sudden death diagnosed with a coronary anomaly at post-mortem, suggesting that a single episode of acute ischemia may lead to sudden death in most of the patients.

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