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Anomalous aortic origin of coronary arteries: Early results on clinical management from an international multicenter study

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ABSTRACT

Background: Anomalous aortic origin of coronary arteries (AAOCA) is a rare abnormality, whose optimal management is still undefined. We describe early outcomes in patients treated with different management strategies.
Methods: This is a retrospective clinical multicenter study including patients with AAOCA, undergoing or not surgical treatment. Patients with isolated high coronary take off and associated major congenital heart disease were excluded. Preoperative, intraoperative, anatomical and postoperative data were retrieved from a common database.
Results: Among 217 patients, 156 underwent *Surgical* repair (median age 39 years, IQR: 15–53), while 61 were *Medical* (median age 15 years, IQR: 8–52), in whom AAOCA was incidentally diagnosed during screening or clinical evaluations. Surgical patients were more often symptomatic when compared to medical ones (87.2% vs 44.3%, $p < 0.001$). Coronary unroofing was the most frequent procedure (56.4%). Operative mortality was 1.3% (2 patients with preoperative severe heart failure).
At a median follow up of 18 months (range 0.1–23 years), 89.9% of survivors are in NYHA ≤ II, while only 3 elderly surgical patients died late. Return to sport activity was significantly higher in *Surgical* patients (48.1% vs 18.2%, $p < 0.001$).
Conclusions: Surgery for AAOCA is safe and with low morbidity. When compared to *Medical* patients, who remain on exercise restriction and medical therapy, surgical patients have a benefit in terms of symptoms and return to normal

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life. Since the long term-risk of sudden cardiac death is still unknown, we currently recommend accurate long term surveillance in all patients with AAOCA.

1. Introduction

Anomalous aortic coronary origin and course represent a rare congenital heart disease (CHD) whose clinical significance has been only recently better appreciated, due to the technical advancement of imaging and epidemiology. In fact, the Anomalous Aortic Origin of Coronary Artery (AAOCA) from the opposite sinus of Valsalva represents the second leading cause of sudden cardiac death (SCD) in healthy children or young athletes, during or immediately after exercise, often with no prodromes [1–6]. Furthermore, an increasing number of children and young adults are being incidentally found to have AAOCA on imaging studies, performed as part of screening campaigns with transthoracic echocardiography (TTE), magnetic resonance imaging (MRI) or for other reasons. Surgical treatment has been widely proposed, aiming at removing any risk of myocardial ischemia and SCD. Single-center studies are based on limited series describing surgical repair as safe and effective [7–13], although late effects on symptoms and risk of SCD are undefined and concerns about the surgical effectiveness remain [14–16].

We report the early results of an ongoing multicentre clinical study including surgical and non-surgical (medical) patients, aimed at determining whether surgical repair for AAOCA is more effective than medical treatment not only in terms of onset major adverse events, but also quality of life.

2. Materials and methods

This is a multicenter retrospective longitudinal study including patients with diagnosis of AAOCA (from 16 different cardiac centers), who were divided in 2 Groups: *Surgical* (patients who underwent surgical repair), and *Medical* (no surgery). Excluded were patients whose diagnosis was done before 1991, and those with isolate high coronary take off, anomalous left coronary artery from pulmonary artery, and association to major CHD (such as tetralogy of Fallot or transposition of the great arteries). Preoperative, intraoperative and postoperative data for the *Surgical* group, and clinical data at diagnosis for the *Medical*, and follow up data for both, were retrieved from a common database. Review of medical records was approved by each hospital local committee on clinical investigation. Individual patients' data were anonymized, and the need for patient consent was waived.

Main characteristics at diagnosis (such as anomalous aortic origin of a right versus left coronary artery-AORCA vs AOLCA-versus "other" variants, anomalous coronary course, associated cardiac disease) are described in detail in Table 1. Diagnostic imaging included TTE, MRI or computer tomography angiography (CTA), and when the anomaly was detected, their results were defined abnormal.

For *Surgical* patients, peri-operative data included surgical technique, associated procedures, postoperative complications, and early death.

Follow up (collected between January 2016 and June 2018) recorded all adverse events (AE- including late death, surgical or interventional procedures); clinical status (NYHA class, persistence of symptoms), progression of aortic valve (AV) regurgitation, return to sports activity. In particular, we defined *coronary related AE* as those involving coronary perfusion or anatomy.

2.1. Statistical analysis

Results are summarized reporting the number and percentage for categorical variables, mean, standard deviation, or median, interquartile range (IQR), minimum and maximum for quantitative variables. Effect of age on outcomes was evaluated by age class subgroups (<10, 11–30, 31–50, >50 yrs). Categorical variables were analyzed with Chi-Squared test and Fisher Exact test according to sample size, while Mann Whitney test was used for quantitative variables. Freedom from death and AE were estimated with the Kaplan-Meier method. Risk factors for early or late death, AE and persistence of symptoms at follow up, which resulted statistically significant at the 5% level were introduced in a multivariable Cox logistic regression. The results are presented as p-value, hazard-ratio (HR) and 95% confidence interval (95% CI).

Table 1
Characteristics of AAOCA patients at presentation.

Variable	All (%)	Surgical (%)	Medical (%)	p-Value
Total	(217)	(156)	(61)	
Female	*93/217 (42.9)*	72/156 (46.2)	21/61 (34.4)	NS
Age (median, IQR)	*37 (13–53)*	39 (15–53)	13 (8–52)	0.063
Type of AAOCA				
AORCA	*138/217 (63.6)*	105/156 (67.3)	33/61 (54.0)	0.084
AOLCA	*49/217 (22.6)*	35/156 (22.4)	14/61 (23.0)	NS
Other	*30/217 (13.8)*	16/156 (10.3)	14/61 (23.0)	**0.03**
Anomalous course				
Interarterial	*182/217 (83.9)*	135/156 (86.5)	47/61 (77.0)	NS
Intramural	*98/217 (45.2)*	98/156 (62.8)	0/61 (0)	<**0.001**
Anterior to pulmonary outflow	*7/217 (3.2)*	1/156 (0.6)	6/61 (9.8)	**0.002**
Intraseptal/retroaortic	*9/217 (4.1)*	4/156 (2.6)	5/61 (8.2)	NS
Other	*19/217 (8.8)*	16/156 (10.3)	3/61 (4.9)	NS
Presence of symptoms	*163/217 (75.1)*	136/156(87.2)	27/61 (44.3)	<**0.001**
Symptoms on effort	*110/217 (50.7)*	103/156(93.6)	7/61 (11.5)	<**0.001**
Chest pain	*55/217 (25.3)*	42/156 (26.9)	13/61 (21.7)	NS
Cardiac arrest	*21/217 (9.7)*	21/156 (13.5)	0/61 (0)	**0.001**
Syncope	*16/217 (7.4)*	14/156 (9.0)	2/61 (3.3)	NS
Dispnea	*14/217 (6.5)*	10/156 (6.4)	4/61 (6.6)	NS
Palpitations	*9/217 (4.1)*	7/156 (4.5)	2/61 (3.3)	NS
Fatigue	*4/217 (1.8)*	4/156 (2.6)	0/61 (0)	NS
Unspecified	*43/217 (19.8)*	38/156 (24.4)	5/61 (8.2)	**0.007**
Preoperative sport activity	*58/217 (26.7)*	44/156 (28.2)	14/61 (23.0)	NS
Prior coronary artery disease	*10/217 (4.6)*	6/156 (3.8)	4/61 (6.6)	NS
Associated cardiac anomalies	*56/217 (25.8)*	33/156 (21.1)	22/61 (36.1)	**0.038**
Aortic valve disease	*18/217 (8.3)*	12/156 (7.7)	6/61 (9.8)	NS
Mitral valve disease	*9/217 (4.1)*	7/156 (4.5)	2/61 (3.3)	NS
Atrial septal defect	*6/217 (2.8)*	4/156 (2.6)	2/61 (3.3)	NS
Other	*23/217 (10.6)*	10/156 (6.4)	13/61 (21.3)	**0.003**

Legend: AORCA, Anomalous aortic origin of right coronary artery from the left sinus; AOLCA, Anomalous aortic origin of left coronary artery from the right sinus; AE, adverse event; NYHA, New York Heart Association.

In order to verify the effects of surgery on outcomes, adjusted effects of covariates (such as anatomy, age, symptoms, etc.) on outcome variables (return to sport activity, NYHA class, symptoms at follow up) were calculated using logistic (for dichotomous variables) or linear (for continuous variables) regression, after propensity score inverse probability weighing, in order to take into account significant differences between the 2 groups. Statistical analyses have been performed with SPSS v23, while Prysm GraphPad v7, Windows/Mac was used for Kaplan-Meier survival curves.

3. Results

We included 217 patients with AAOCA: 156 patients (71.9%) were *Surgical*, while 61 (28.1%) were *Medical* (Table 1). AOLCA and AORCA were present in 22.4% and 67.3% in surgical patients, and in 23.0% and 54.0%, respectively in medical ones, with no significant differences (Table 1).

3.1. Surgical group

Surgical repair was performed in most AOLCA (even in asymptomatic, especially in active patients and <30 yrs), and in symptomatic AORCA (or with a positive provocative test or young age). Among 156 surgical patients, interarterial course was reported in 86.5%, and intramural in 62.8%. Symptoms were present in 136 patients (87.2%, Table 1): of these, 90 (66.2%) had intramural course, and 103 (66.0%) were effort related. Twenty-one patients had emergent admission for aborted SCD (15 in AORCA, 5 in AOLCA and 1 in other; one required ECMO followed by a successful coronary artery reimplantation).

Most frequent abnormalities at ECG were ST elevation in 7 patients, Q waves in 6, and right bundle branch block in 2; TTE and CTA multislice (95.5% and 72.4%, respectively) were diagnostic in 37.6% and 86%, respectively, and provocative exercise and nuclear stress tests were performed occasionally (Supplementary Table 1).

Surgical procedures are described in detail in Supplementary Tables 2 and 3. Unroofing procedure was the most frequent technique (56.4%), followed by reimplantation (19.2%) and coronary artery bypass graft (15.4%); other techniques were used in 9% of cases, and included the Vouhè reimplantation [17] in 3 cases.

Operative mortality was 1.3% (2 patients): one 44 years old patient (intramural AOLCA) was emergently admitted for aborted SCD during exercising, and died 15 days after Vouhè reimplantation, due to low cardiac output syndrome (LCOS); a 1 year old infant (left anterior descending from right coronary sinus, with preoperative EF < 20%) died 61 days after CABG, for multiorgan failure and mechanical cardiac support (MCS).

Twenty-two post-operative major complications occurred in 14 pts (9%, Supplementary Table 2). Among 7 patients who required an early reintervention, an 11 years old patient (AOLCA, interarterial course) underwent heart transplant after MCS. All 154 survivors were discharged home on aspirin, in good clinical conditions; 2 patients (1.3%) were discharged home with less than moderate AV regurgitation after unroofing.

3.2. Medical group

Anatomical characteristics and associated anomalies are shown in Table 1. These patients did not undergo AAOCA surgery, because of absence of symptoms correlated to anomalous coronary anatomy, negative provocative stress test, low risk anomalous coronary anatomy, age < 15 years or >60 years, or patient's choice. As in the surgical group, AORCA occurred more often (54%, Table 1). Other anatomical variants (23%) were significantly more frequent than in surgical patients (p 0.03), and were: anomalous origin with high take off of the right coronary from the left sinotubular junction (5), single coronary (4), left anterior descending from right sinus (4) and circumflex from right sinus (1); 47 patients presented with interarterial course, while none was intramural. Symptoms were reported in 27 patients (44.3%, in 7 were effort related), mostly >50 yrs. There were no aborted SCD. Diagnosis was done during cardiovascular procedures in 5 patients (coronary stenting in 3, and valve surgery in 2).

Baseline ECG was available in 54 patients, and was normal in 40. Most frequent ECG abnormalities were ST elevation in 6 and atrial fibrillation in 2 (Supplementary Table 1).

4. Late outcomes

At a median follow up time of 18 months (IQR: 6–48, range 1 month–23 years, 88.9% complete, Table 2), there were 3 late deaths (2.2%) in 3 > 70 years old (AORCA and interarterial course, 2, other, 1), after 1, 60 and 102 months from surgery (CABG in all). There were no deaths in *Medical* patients.

4.1. Surgical group

Among 133 early survivors, 9 other major AE occurred in 8 patients (6.0%) after a median time of 9 months (IQR 6–69, range 1–80 months); 3 patients (2.3%) required a surgical reoperation and 5 (3.7%) required a non-surgical procedure (Table 2). However, only 5 were coronary related AE (coronary artery stenting in 3, AICD implantation in 1, surgical resection of an intramyocardial bridge in 1). Most late survivors (120, 91.2%) were in NYHA class I and II, and 48.1% (younger patients) returned back to sports activity. Follow up evaluation tests are summarized in Supplementary Table 4. Persistent symptoms (mostly unspecified chest pain) correlated to positive stress test in 1 patient only, while 2 patients had concomitant arrhythmias and hypertension.

4.2. Medical group

Major AE occurred in 4 patients (valve surgery, 2, PDA closure, 1; ASD closure, 1), but none was coronary related. After diagnosis, 18.2% (vs 23% before diagnosis) continued recreational sports activity. Chest pain was present at diagnosis and persisted in 5 patients, 4 of whom were older than 50 years. Twenty patients (36.7%) were on beta blockers. Follow up evaluation tests are summarized in Supplementary Table 4.

4.3. Statistical analysis

Analysis of categorical variables with Fisher Exact test showed that symptoms were significantly more frequent in *Surgical* patients (85.9% vs 44.3%, p 0.001, Table 1). Furthermore, occurrence of overall and coronary related AE resulted not significantly different in the 2 groups (p 0.31, Table 2).

Propensity score inverse probability weighting (Table 3) confirmed that surgery was effective in allowing patients to return to normal unrestrained life and sport activity (p < 0.001).

Multivariable logistic regression analysis (Supplementary Table 5) demonstrated that in *Surgical* patients return to sport activity was significantly higher in younger patients, while AE were not significantly different among anatomical variants of AAOCA and age classes; unroofing technique seemed to be protective from overall incidence of AE in the long term (p 0.02, OR 0.31, Supplementary Table 5).

5. Discussion

This is the largest multicenter retrospective clinical study ever reported on early outcomes of different management (namely, surgical treatment versus clinical observation) of AAOCA. We demonstrate that surgical treatment has a very low operative risk, and surgical patients can go back to unrestrained life more often than medical ones. No significant difference in survival or incidence of AE in the 2 groups was found at a short term follow-up.

Prevalence of AAOCA is still uncertain. Angelini et al. [18] reports a frequency of high risk anomalous coronaries as high as 0.44% in a

Table 2
Clinical data at follow up.

Variable	All (%)	Surgical (%)	Medical (%)	p-Value
Follow up completeness	193/217 (88.9)	138/156 (88.5)	55/61 (88.7)	NS
Alive	188/217 (86.7)	133/156 (86.4)	55/55 (100)	NS
Age	35 (15–54)	38 (18–55)	15 (9–52)	**0.045**
Persistent symptoms	29/188 (15.4)	24/133 (14.2)	5/55 (9.1)	NS
Chest pain	15/188 (79.8)	10/133 (7.5)	5/55 (9.1)	NS
Dyspnea	3/188 (1.6)	3/133 (2.3)	0 (0)	NS
Fatigue	3/188 (1.6)	3/133 (2.3)	0 (0)	NS
Syncope	1/188 (0.5)	1/133 (0.8)	0 (0)	NS
Palpitations	1/188 (0.5)	1/133 (0.8)	0 (0)	NS
Dizziness	1/188 (0.5)	1/133 (0.8)	0 (0)	NS
Unspecified	5/188 (2.7)	5/133 (3.8)	0 (0)	NS
Performing sport	74/193 (39.3)	64/133 (48.1)	10/55 (18.2)	<**0.001**
Length of follow up (median yrs, IQR, range min–max)	1.5 (0.5–2) [0−23]	2.1 (0.7–4.5) [0–23]	1.2 (0.5–2.7) [0−10]	**0.045**
NYHA ≥ II	19/188 (10.1)	13/133 (9.8)	6/55 (10.9)	NS
AE	18/188 (9.6)	12/133 (9.0)	6/55 (10.9)	NS
Interventional	8/188 (4.3)	6/133 (4.5)	2/55 (3.8)	NS
Surgical	5/188 (2.7)	3/133 (2.3)	2/55 (3.6)	NS
Late death	3/193 (1.6)	3/138(1.6)	0/55 (0)	NS
Coronary related AE (excluding late death)	**3/188 (1.6)**	**3/133 (2.3)**	**0/55 (0)**	**NS**
Overall mortality	5/193 (2.6)	5/138 (3.6)	0/55 (0)	NS

Legend: AE, adverse event; NYHA, New York Heart Association.

population of middle and high school healthy volunteers. As described in other studies [1–6,18–20], we also found that interarterial AORCA was 3 times more frequent than AOLCA.

Clinical interest towards AAOCA has recently increased as various studies reported this anatomical entity as the second cause of SCD in young competitive athletes [3–5,21]. Wren et al. [22] reported 270 cases of SCD among 800.000 patients, with a presumptive number of about 800–1600 individuals with AAOCA. However, none of those SCD was related to AAOCA at postmortem evaluation. On the contrary, Maron [21] reported 119 cases among 1866 episodes of SCD related to presence of AAOCA (about 11%). These numbers have been reported among patients practicing high level of physical activity [4–6]. Thus, rate of SCD may be expected to be somewhat lower in the general population, which is not necessarily practicing high level sports. In addition, there are some anatomical AAOCA variants which have a lower risk of SCD (such as circumflex from the right sinus) and do not need surgery.

To determine whether AAOCA is best treated by surgical repair or clinical observation and exercise restriction, we should be able to demonstrate the safety of surgical repair in terms of early mortality and morbidity, while its true effectiveness is demonstrated only by a greater freedom from SCD or AE in the long term, when compared to controls. Mery et al. [23] have used the decision analysis method to evaluate the impact of 3 different strategies (surgery, observation, exercise restriction) on outcomes of patients with AAOCA. This study supports surgery as optimal strategy in patients <30 years with AOLCA, while observation resulted as the best option in AORCA if >25 years of age. Thus, the optimal management for such patients depends on multiple factors (type of AAOCA, age, symptoms, etc.) and decision analysis is a tool to understand how these characteristics may affect the outcomes.

Table 3
Inverse probability of treatment weighting (propensity score) between *Surgical* vs *Medical* at FU.

	Surgical (%)	Medical (%)	p-Value
Sport activity	64/133 (48.1)	10/55 (18.2)	<**0.001**
Symptoms	24/133 (18.0)	5/55 (9.1)	0.086
NYHA ≥ II	14/133 (10.5)	6/55 (10.9)	NS

Legend: AE, adverse event; NYHA, New York Heart Association.

In our study, we could clearly demonstrate that surgery (especially unroofing and reimplantation) is safe, with only 2 early deaths occurring in patients with severe preoperative cardiac dysfunction. In our experience, surgical indication was in accordance with the most accepted expert consensus surgical guidelines [24,25], despite some intercenter variability. As in other surgical series [10–14], unroofing of the intramural segment was the commonest procedure (56.4%), whose protective effect from AE (OR 0.31, Table 3) is to be related to excision of the intervening roof of the intramural segment, (causing coronary compression and ischemia during effort), the enlargement of the slit like orifice and its relocation to the appropriate sinus, and the elimination of the interarterial course. Coronary reimplantation was favoured when the intramural segment was too short or absent, while CABG procedure was performed in 24 patients at a significantly higher age. As reported by Fedoruk et al. [26], late graft occlusion can occur after CABG, probably because most patients have a normal coronary blood flow at rest preoperatively, and competitive flow may jeopardize the internal mammary artery long term patency. However, CABG alone may be a valuable option when other procedures are contraindicated, such as in anomalous vessels with severe proximal narrowing, or in older patients with diffuse atherosclerosis.

Interesting enough, nearly half of surgical patients have returned to preoperative sport activity and unrestricted lifestyle, at a significantly higher frequency than medical ones (Table 3). This shows that surgical repair, despite it is not proved to alleviate the risk for detrimental future events yet, allows patients to resume desirable activities and normal life-style, critically important from the perspective of their perception for quality of life (QoL). This is in accordance with the current recommendations by the American Heart Association and American College of Cardiology [27], which suggest that "after successful surgical repair of an anomalous origin from the wrong sinus, athletes may consider participation in all sports 3 months after surgery if free of symptoms and exercise stress test shows no evidence of ischemia or cardiac arrhythmias".

On the other hand, *medical* patients have a restricted lifestyle, which may impact their own and families QoL, as reported by Sing et al. [28], who demonstrated that patients' families were often experiencing a decreased level of general health and emotional and physical QoL scores. To minimize this, exercise restriction should be better defined and families should be better counselled, to understand that their children

can participate in most activities. Recent expert consensus guidelines [25] are less restrictive with asymptomatic patients, and patients with asymptomatic AORCA and negative stress test, after SCD risk councelling, may participate to competitive sports.

It is of interest to underline that in our series CT scan diagnosis was highly reliable, while echocardiographic one was still operator dependent (Supplementary Table 2). Lastly, there is no evidence of a better freedom from AE in surgical patients yet, mostly because of the short follow up. However, despite occurring in few elderly patients, they were not clear in etiology, and the surgical manipulation of coronary arteries and ostia justifies concern for potential late stenosis due to scarring.

5.1. Limitations

Major limitations are the relatively small numbers, and the short follow up time which does not allow to assess the real impact of surgery on late outcomes, compared to the clinical observation.

6. Conclusions

Surgery for AAOCA is safe with a low incidence of operative deaths and morbidity, which may be related to preoperative conditions.

However, patients who underwent medical treatment did not differ in terms of early survival or AE. Thus, the claimed protective effect of surgery cannot be demonstrated yet.

Nonetheless, surgery does provide an important benefit in terms of returning to normal activity, when compared to *Medical* patients, who remain on exercise restriction and medical therapy.

Since the remaining risk of sudden cardiac death is still unknown, and occurrence of late adverse events after surgery is not negligible, an accurate long term surveillance in all patients with AAOCA is mandatory.

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Conflict of interest

None declared.

Appendix A. Supplementary data

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