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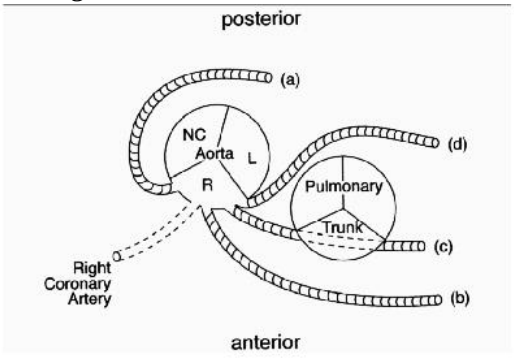
**The Intramural course of anomalous coronary arteries: a high-risk characteristic?**

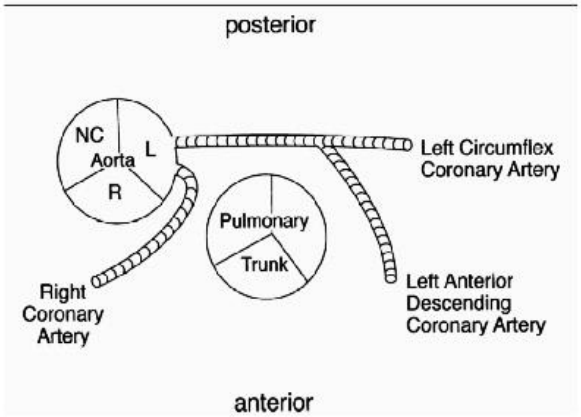
## A. Study Purpose and Rationale

Anomalies of coronary arteries, both in origin and course, were first described approximately 2000 years ago by Greek physician Galen of Pergamum, with Vesalius later providing illustrative representations of aberrant coronary artery anatomy in his 16th century work, *Tabulae Anatomica*.[1] While some variability is noted, congenital anomalies of the coronary arteries are reported to occur in 0.6% - 1.3% of the general population.[2,3] Coronary artery anomalies may occur concurrently with other congenital heart defects or as an isolated abnormality. The clinical manifestations and significance of coronary artery anomalies varies considerably. Certain coronary artery anomalies are discovered incidentally, remaining clinically silent, and for the most part, benign. However, at the other end of the spectrum are anomalies which may cause angina, dyspnea, syncope, arrhythmias, myocardial infarction, and sudden death.

Anomalous aortic origin of a coronary artery (AAOCA) from the incorrect coronary sinus of Valsalva is a relatively rare congenital anomaly that has been associated with an increased risk of sudden death.[4,5] Two of the most important subtypes are those in which the left main coronary artery originates from the right sinus of Valsalva (ALMCA) or the right coronary artery originates from the left sinus of Valsalva (ARCA) [Fig. 1]. In a majority of these abnormalities the anomalous coronary artery takes an intramural course, traveling within the aortic wall, between the aorta and pulmonary artery, before leaving the aortic wall from the correct sinus. Both of the aforementioned defects (ALMCA and ARCA), especially those demonstrating an intramural course, have been associated with sudden cardiac death.[5] The risk of sudden cardiac death appears to be more pronounced in young athletes and those subject to strenuous exertion, however no study has been able to accurately predict the true risk of sudden death from an ALMCA or ARCA. The incidence of ALMCA and ARCA in the general population is a controversial and often disputed topic. Autopsy studies have provided a combined incidence of 0.17%, while angiographic series have offered estimates ranging between 0.1% - 0.3%.[6,7] Sadly, the diagnosis of




Possible courses of an anomalous left coronary artery from the right sinus of Valsalva. After arising from the right sinus of Valsalva, it may course (a) posterior to the aorta, (b) anterior to the right ventricular outflow tract (which is located directly below the pulmonary trunk), (c) within the interventricular septum, or (d) between the aorta and the right ventricular outflow tract. The latter is associated with sudden cardiac death.




An anomalous right coronary artery may arise from the left sinus of Valsalva, after which it may course between the aorta and pulmonary trunk.

Fig. 1 – Illustration of possible configurations for ALMCA and ARCA

AAOCA is often first made during post mortem studies, as sudden death is commonly the initial manifestation of the defect in what is mostly an asymptomatic patient population. Studies have shown that only between 18 – 30% of patients with anomalous coronary arteries present with cardiovascular symptoms, such as chest pain, syncope, or dyspnea.[8,9]

Sudden death in these patients likely occurs because of a reduction in blood flow in the anomalous vessel, resulting in myocardial ischemia or infarction.[6] Several mechanisms have been proposed attempting to explain the pathophysiology of reduced coronary blood flow in these patients. As a result of the acute take off which the anomalous coronary artery often takes, the ostium of the anomalous artery is slit-like, rather than round as in its normal counterpart. During systole the slit-like orifice may become further compressed, thus occluding further blood flow. Also suggested is that kinking or torsion of the anomalous artery may occur as it courses between the great vessels. Another explanation which has been hypothesized proposes that the intramural path within the aortic wall, which many cases demonstrate, is a potentially lethal condition as compression of the coronary artery may occur during times of increased aortic pressure, such as during exercise. It is likely that multiple factors contribute to the precipitation of myocardial ischemia, infarction, and sudden cardiac death in cases of AAOCA. While multiple studies have examined various characteristics of the anomalous arteries in an attempt to identify "high-risk" defects, they have, for all intensive purposes, been unable to assess to the true risk of sudden death for patients with AAOCA.[10]

For patients who receive the diagnosis of ALMCA or ARCA, one must immediately consider the treatment options. While medical management is an option, surgery remains the most widely used and advocated approach. [6, 11, 12, 13] Currently there is general agreement among most physicians that if a patient is symptomatic or shows evidence of ischemia in the presence of an ALMCA or ARCA, surgery should be offered, especially in patients under the age of 30.[5,10] A grey area, however, exists when considering treatment options for asymptomatic patients with incidentally discovered AAOCA. Some argue that surgical management is mandatory in young patients with AAOCA, regardless of the presence of symptoms.[5] Many surgeons believe that since AAOCA is a potentially lethal abnormality, with a documented association with sudden cardiac death, surgical correction is indicated in all patients who can tolerate the procedure. They contend that subjecting patients to a known risk of sudden death is unnecessary.

There are those, however, who believe that there are few, if any, indications for surgical intervention in asymptomatic patients.[14] Physicians opposed to surgical management of asymptomatic AAOCA patients cite the lack of outcomes-based evidence, the absence of knowledge of true risk of sudden cardiac death, the deficiency of risk stratification in asymptomatics, and the uncertainty of the pathophysiology which leads to sudden death in these patients. It is not currently known if the risk of surgical intervention, while quite low, outweighs the true risk of sudden death in asymptomatic patients carrying the diagnosis of AAOCA. While the answer is certainly not clear at the present date, the question remains: "How does one actively manage asymptomatic patients with known AAOCA?"

In this study we plan to investigate a single, anatomic characteristic, the length of the intramural segment of the anomalous coronary artery, in an attempt to identify a high-risk characteristic, which may assist in risk stratification of patients diagnosed with anomalous coronary arteries. We hypothesize that there is an association between the length of the intramural coronary artery segment and the risk of sudden cardiac death. Presently, no study has clearly described an anatomical or structural explanation as to why patients with AAOCA succumb to sudden death. With this study, we hope to contribute to a greater understanding of the pathophysiology involved in this syndrome, and to ultimately improve management of patients diagnosed with AAOCA as prospective identification of high-risk characteristics within the proximal course of the anomalous coronary artery will allow timely surgical correction.

**B. Study Design, Procedure and Statistical Analysis**

This study will be a pathological study using post-mortem cardiac specimens. Utilizing the Department of Pathology at Columbia University we plan to identify and obtain all specimens containing anomalous left and right coronary arteries originating from the contralateral sinus of Valsalva and containing an intramural segment coursing between the aorta and main pulmonary artery. Furthermore, the medical records corresponding to the appropriate specimens will be examined to determine the cause of death. After reviewing the available data, the cause of death will be assigned by consensus of the investigators.

Sudden cardiac death shall be defined as death which occurred within one hour of the onset of cardiovascular symptoms such as syncope, chest pain, and dyspnea. Patients defined as having succumbed to sudden cardiac death may not demonstrate the presence of any other cardiac anomalies, coronary artery atherosclerosis, or other conditions which may result in sudden death. Furthermore, toxicology studies may not reveal the presence of any illicit substances which could be responsible for the patient's death.

After the heart specimens are acquired, two measurements will be obtained. First, the circumference of the aortic root will be measured. Next, the length (in millimeters) of the intramural segment of proximal coronary artery course within the aortic wall will be obtained. The measured values will be expressed as the "*intramural ratio*," calculated as follows:

$$\text{Intramural ratio} = \frac{\textit{length of coronary artery within aortic wall } (mm)}{\textit{circumference of aortic root } (mm)} \qquad (1)$$

Data will be analyzed for the association of the *intramural ratio* with the cause of death (anomaly related sudden cardiac death versus non-anomaly related death). As a continuous variable, equality of means will be evaluated utilizing the Student *t* test. A two tailed p value of $\leq 0.05$ will be judged to be statistically significant.

Being a retrospective, pathological examination of post mortem specimens, this study shall be limited by the fixed number of specimens available in the Department of Pathology. Hence , the power analysis in this investigation will be used to determine the smallest difference for which the available number of subjects will lead to statistical significance at a power of 80% and p = 0.05. As this study has not been attempted previously, the literature contains no measurements of the average intramural length nor the standard deviation and thus currently the effect size may only be calculated in terms of the standard deviation. As there is no cross-over between groups, an unpaired *t*-test will be used. Assuming that the number of specimens ($n_i$) in each group is equal ($n_1 = n_2$), one obtains:

$$n_i = 1 + 16\left(\frac{\sigma}{\varepsilon}\right)^2 \qquad (2)$$

where $n_i$ = number of subjects in the $i^{th}$ group; $\sigma$ = standard deviation of mean; $\varepsilon$ = the effect, postulated difference in outcome measure

Solving for the effect, $\varepsilon$, yields:

$$\varepsilon = \frac{4}{\sqrt{n_i - 1}}\sigma \qquad (3)$$

Utilizing Eq. 3, one is able to construct a table determining the smallest difference for which a given number of subjects will lead to statistical significance, at the given power and p-value. Table 1 details the results of such calculations.

| $n_i (n_1 = n_2)$ | ε (in terms of σ) |
|---|---|
| 10 | 1.3σ |
| 15 | 1.1σ |
| 20 | 0.92σ |
| 25 | 0.82σ |

Table 1 – Determination of detectable effect size given the number of subjects in a group (power =80%, p≤0.05)

**C. Study Drugs**

No study drugs will be administered during the course of this study.

**D. Medical Devices**

No medical devices will be used during the course of this study.

**E. Study Questionnaires**

No study questionnaires are required by this study.

**F. Study Subjects**

This study will utilize post mortem cardiac specimens from the Department of Pathology at New York-Presbyterian Hospital. Studies will be chosen without regard to sex or ethnic background.

*Inclusion Criteria*

- Isolated anomalous aortic origin of a coronary artery (AAOCA) from the incorrect coronary sinus of Valsalva without any evidence of other congenital or structural heart defects.
- Intact proximal course of the anomalous coronary artery containing an intramural segment located between the aorta and main pulmonary artery.
- Intact aortic root

**G. Recruitment**

This is a post mortem study and no patient recruitment is necessary.

**H. Confidentiality**

Confidentiality will be protected using the standard CUMC clinical protocol procedures outlined by the CUMC IRB and HIPAA.

**I. Potential Conflict of Interest**

None

**J. Location of the Study**

This study will be conducted in the laboratories of the Department of Pathology at CUMC. Data analysis will occur in the Division of Pediatric Cardiac Surgery at the Children's' Hospital of N.Y.

**K. Potential Risks**

As this is a post mortem, pathological study, there are no direct risks to any patients.

**L. Potential Benefits**

As this is a post mortem study there is no chance that the patients involved in the study will benefit. However, with this study we hope to contribute to a greater understanding of the pathophysiology involved in this syndrome, and to ultimately improve the management of patients diagnosed with AAOCA in the future.

**M. Alternative Therapy**

N/A

**N. Compensation to Subjects**

N/A

**O. Cost to Subjects**

N/A

**P. Radiation or Radioactive Substances**

N/A

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