Prevalence and characteristics of CAAs in the black sea region

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Abstract
Aim: To date there has been no data about the prevalence of coronary artery anomaly (CAA) in the Turkish population of the Black Sea Region who underwent trans-radial coronary angiography. We aimed to determine the frequency and characteristics of CAA in our patients. Material and Method: All the coronary angiographies performed from September 2015 to September 2016 in our hospital were reviewed. Demographic characteristics and laboratory parameters of patients were reviewed retrospectively from the patients’ data set. A total of 1617 patient were included in our study. Results: CAAs were found in 73 patients (4.51%), of whom 41 (56.16%) had intrinsic coronary artery anatomy. Twenty-two (30.13%) patients had anomaly of origination and course and 10 (13.69%) patients had anomaly of coronary artery termination. The mean age was 59.35±11.86 in the study group and 60.11±6.61 in the control group. Myocardial bridge was the most common anomaly in our study with a prevalence of 2.16%. Absent LMCA was the second most common anomaly in our study with a prevalence of 0.80% and coronary artery fistula was third with a prevalence of 0.61%. Discussion: We found the prevalence of CAAs among the Turkish population of the Black Sea Region to be similar to previously published studies from our country. To avoid misunderstandings one must know the normal anatomy of coronary vasculature, variations, and the anomalies. When coronary angioplasty or cardiac surgery is planned in patients with CAA, special attention must be paid not to harm coronary arteries in unexpected locations.

Keywords
Coronary Artery Anomaly; Trans-Radial Coronary Angiography; Black Sea Region

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Introduction

Coronary artery anomaly (CAA) is one of the main reasons for sudden cardiac death among young athletes. CAA is not completely understood and its importance has been neglected so far. CAA is defined as coronary arteries not fulfilling the criteria of normal coronary artery anatomy. Angelini has proposed that 99% of the population (2 to 3 standard deviations) can be assumed to have variations within normality (normal variants) and that the remaining 1% of population (outside 2 to 3 standard deviations) could be assumed to have CAA [1]. Despite this assumption there is no real world data to support this statement. Data about the prevalence of CAA comes from post mortem autopsy series of deaths with unspecified causes and coronary angiographies of symptomatic patients. Data derived from the autopsy series showed a relatively lower incidence of up to 0.03% [2] and data derived from the coronary angiography series showed an incidence up to 5.6% [3].

Coronary arteries arise from the sinus of Valsalva (SoV) just above the aortic valve from the ascending aorta to supply the myocardium. Two main trunks of coronary arteries share normal myocardium perfusion: left main coronary artery (LMCA) and right coronary artery (RCA). LMCA arises from the left SoV and divides into left anterior descending artery (LAD) and circumflex artery (CX). However, occasionally LMCA divides into three vessels: intermediate artery (IM) additional to LAD and CX. LAD follows the anterior interventricular groove to the apex of the heart while supplying anterior and lateral of the left ventricle (LV) with diagonal branches and the septum with septal branches. CX follows the left atrioventricular groove posteriorly while supplying the lateral and free wall of LV with obtuse marginal (OM) branches and inferior wall of LV with posterior descending artery (PDA) in about 15% of patients. When IM is present, it supplies the free wall of LV where diagonal and OM could not. RCA follows the right atrioventricular groove posteriorly while supplying right ventricle (RV) with RV branches and LV inferior with PDA in about 85% of general population.

Most of the coronary anomalies permit normal myocardial development and function, resulting in a normal life expectancy. Moreover, intense athletic activity could be performed while having a coronary anomaly. However, there is a wide range of symptoms and pathologies considered to lead to sudden cardiac death that are associated with coronary anomalies. Myocardial ischemia associated clinical presentations in CAA include chest pain, sudden death, cardiomyopathy, syncope, dyspnea, ventricular fibrillation, and myocardial infarction. Volume overload, increased risk of bacterial endocarditis, increased risk of secondary aortic valve diseases, difficulties during diagnostic angiography or procedural angioplasty and increased risk of complications during cardiac surgery are the other inconveniences of coronary anomalies [3].

The purpose of this study was to determine the prevalence of origination, course, and termination anomalies of coronary arteries among Black Sea Region Turkish population who underwent trans-radial coronary angiography for any reason.

Material and Method

Study Design and Patient Selection

This is a single center retrospective study compromising all the patients who underwent coronary angiography from September 2015 to September 2016 in our tertiary university hospital. A total of 1899 coronary angiographies were performed during this interval. Two hundred eighty-two patients were excluded from the study according to the exclusion criteria, which were as follows:

i). Patients under 18 years old,

ii). Previous cardiac surgery,

iii). Inconclusive coronary images,

iv). Patients complicated with cardiopulmonary arrest,

v). Patients with connective tissue disorder,

vi). Patients with coronary anomalies associated with complex congenital heart disease,

vii). Patients with one or more totally occluded epicardial coronary artery.

viii). Patients who underwent coronary angiography through the trans femoral route.

Coronary Angiography Evaluation

All the coronary angiography images were evaluated by two interventional cardiologists and coronary artery anomalies were diagnosed by consensus. Patients were excluded when it was impossible to make a diagnosis. Coronary artery anomalies were defined and classified according to the classification proposed by Angelini. All the coronary angiography images were investigated for anomalous take off from aorta, abnormal course (myocardial bridges), abnormal termination (coronary fistulas), and abnormal coronary collateral arteries.

The coronary images were further evaluated for i) absence of left main coronary artery (separate ostia of LAD and CX), ii) atypical beginning of LAD (arising from right aortic sinus or RCA), iii) atypical beginning of CX (arising from right aortic sinus or RCA), and iv) atypical beginning of RCA (arising from left aortic sinus, arising from CX or presence of split RCA which could be defined as two different RCA originating from right aortic sinus or splitting of RCA into two duplicates shortly after arising from right aortic sinus).

Myocardial bridge diagnosis was made according to the presence of 30% or more systolic compression of coronary arteries that resolve in diastole. When more than one myocardial bridge is present in the same coronary artery it is accepted as a single myocardial bridge.

Coronary artery fistulas were investigated attentively for their origin, course, and termination. When there were two different anomalies (e.g., presence of MB and split RCA or coronary artery fistula and split RCA) in the same patient, it was accepted as a single patient but two different anomalies.

Three experienced interventional cardiologists performed all the coronary angiographies according to current guidelines through the right radial route.

Patient Demographic Characteristics, Laboratory Parameters, and Ethics Approval

Demographic properties and laboratory parameters of the patients were obtained from the patients’ data set. All the blood samples were drawn one or two days prior to the procedure in elective patients and within 2 hours in patients with unstable
angina, non ST-elevation myocardial infarction, and ST-elevation myocardial infarction.

The study was approved by the Ethics Committee of the University.

**Statistic Analysis**

The SPSS statistical software package (SPSS, version 19.0 for windows; SPSS Inc., Chicago, IL, USA) was used for all the statistical calculations. Continuous variables were expressed as mean ± S.D.; categorical variables were shown as percentages. Student’s t-test was used to compare continuous variables whereas chi-square was used to compare categorical variables. For all the tests, a value of p<0.05 was considered to be statistically significant.

**Results**

A total of 1617 consecutive patients were included in our study. Seventy-three of them (4.51%) were found to have CAA. Twenty (27.39%) of the CAA patients and 445 (28.82%) of the control patients were female. Mean age was 59.35±11.86 in the study group and 60.11±6.61 in the control group. Groups were similar in relation of cardiovascular risk factors (Hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), smoking, body mass index (BMI), chronic kidney disease (CKD), previous coronary artery disease (CAD), stroke, and baseline biochemistry (glucose, TSH IU/dL, eGFRC-G, creatinine) and hematological (hematocrit (HCT), white blood cell count (WBC), platelet count) factors (Table 1).

Coronary artery anomalies were classified according to the systemic anatomic classification proposed by Angelini (1). Seventy-three patients of the total 1617 patients were identified as having CAA, with a prevalence of 4.51%. Of these 73 patients, 41 (56.16%) were found to have anomaly of intrinsic coronary artery anatomy; 22 (30.13%) patients were found to have anomaly of origination and course; and 10 (13.69%) were found to have anomaly of coronary artery termination (Table 2).

Myocardial bridge was the most common anomaly in our study with a prevalence of 2.16%. Absent LMCA was the second most common anomaly in our study with a prevalence of 0.80%. Prevalence of other anomalies were as follows: coronary artery fistula at 0.61%, CX arising from right anterior sinus at 0.18%, RCA arising from left anterior sinus at 0.12%, absent OM at 0.12%, woven coronary anomaly at 0.12%, LMCA arising from right anterior sinus at 0.061%, RCA arising from non coronary sinus at 0.061%, PDA arising from right anterior sinus at 0.061%, single coronary artery at 0.061%, dual LAD at 0.061%, and coronary crossing at 0.061% (Table 3). Four patients had more than one anomaly. One patient had both LAD and RCA fistulas, another had RCA fistula and myocardial bridge. One patient had woven coronary anomaly in OM and IM. One patient had myocardial bridge and coronary crossing. In these patients each anomaly was included in its own group separately.

**Table 1. Demographic characteristics, risk factors identification and baseline laboratory parameters of patients.**

<table>
<thead>
<tr>
<th></th>
<th>CAA (n=73, 4.51%)</th>
<th>Controls (n=1544, 95.48%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.35±11.86</td>
<td>60.11±6.61</td>
<td>0.478</td>
</tr>
<tr>
<td>Sex (Female, (%))</td>
<td>20 (27.39%)</td>
<td>445 (28.82%)</td>
<td>0.793</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.83±4.22</td>
<td>27.17±2.37</td>
<td>0.511</td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>43(58.90%)</td>
<td>891 (57.70%)</td>
<td>0.904</td>
</tr>
<tr>
<td>Diabetes mellitus, (%)</td>
<td>21(28.76%)</td>
<td>457 (29.59%)</td>
<td>0.879</td>
</tr>
<tr>
<td>Hyperlipidemia, (%)</td>
<td>15(20.54%)</td>
<td>318 (20.59%)</td>
<td>0.914</td>
</tr>
<tr>
<td>Smoking, (%)</td>
<td>19(26.02%)</td>
<td>313 (20.27%)</td>
<td>0.234</td>
</tr>
<tr>
<td>Chronic kidney disease, (%)</td>
<td>6(8.21%)</td>
<td>117 (7.57 %)</td>
<td>0.820</td>
</tr>
<tr>
<td>Stroke, (%)</td>
<td>3(4.10%)</td>
<td>704 (43.53%)</td>
<td>0.865</td>
</tr>
<tr>
<td>CAD, (%)</td>
<td>15(20.54%)</td>
<td>293 (18.97%)</td>
<td>0.738</td>
</tr>
<tr>
<td>Hematocrite, %</td>
<td>40.8±5.6</td>
<td>40.9±4.8</td>
<td>0.841</td>
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<tr>
<td>White Blood Cell, 10³/µL</td>
<td>8.9±4.3</td>
<td>8.1±3.1</td>
<td>0.140</td>
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<tr>
<td>Platelet count, 10³/µL</td>
<td>253±93</td>
<td>240±69</td>
<td>0.130</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>98±48</td>
<td>101±39</td>
<td>0.755</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.78±0.10</td>
<td>0.81±0.07</td>
<td>0.228</td>
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<tr>
<td>e-GFRc-G</td>
<td>104±13</td>
<td>106±6</td>
<td>0.850</td>
</tr>
<tr>
<td>TSH IU/dL</td>
<td>2.1±1.6</td>
<td>2.3±1.1</td>
<td>0.532</td>
</tr>
</tbody>
</table>


**Discussion**

The present study found that 4.51% of Turkish patients from the Black Sea Region who underwent trans-radial coronary angiography for any reason have CAAs according to Angelini’s definition (origination, course, and termination anomalies of coronary arteries). Anomaly of intrinsic coronary artery anatomy was the most frequently seen with 56.16% whereas the
frequency of anomaly of origination and course was 30.13% and the frequency of anomaly of coronary artery termination was 13.69%. The prevalence of CAAs was reported to vary from 0.2% to 8.4% in previous studies [4, 5]. Our study was in harmony with previous studies in relation to the frequency of CAA. However, our prevalence findings were higher than those in the previously conducted studies from our country [6-9]. This difference was attributed to variability of the classification of CAA from study to study. Myocardial bridge, one of the most frequently seen anomalies of coronary artery anatomy, was not accepted as an anomaly and excluded from some studies [10]. Another explanation for this discrepancy could be variability of CAAs between regions in a country and between countries. Baseline characteristics of the patients were similar among groups in our study. The prevalence of HT was similar to previously published studies [11]. However, DM was found to be more common than in previously published studies from our country [12]. This was attributed to an older and selected population for higher risk of having CAD. Previous CAD prevalence was similar between groups. Despite contradictory ideas about the association of CAA with obstructive CAD, it is generally accepted that normal segments of coronary arteries of a person with anomalous course have a similar risk of developing obstructive coronary artery disease. Hematologic and biochemistry parameters were similar between groups in our study. Similar demographic and laboratory characteristics between groups make it difficult to predict which patients may have CAAs.

**Myocardial bridge (Figure 1: A-B)**

Incidentally found during a selective coronary angiography or at autopsy, CAAs exist as early as birth and are thought to have a genetic background [10, 13, 14]. The real prevalence of CAAs is not known. The range of prevalences reported in the literature may be above or under the real prevalence based on the classification of CAAs and selection bias. Myocardial bridge, once believed to be a benign condition, is a passage of a part of an epicardial coronary artery under the myocardium that can compromise blood flow during systole. LAD is the most affected coronary artery. Location and length of the myocardial bridge, thickness of myocardium, and the degree of cardiac contractility are the main determinants of systolic compression. Sudden cardiac death [15], exercise-induced atrio-ventricular conduction block [16], stunning [17], arrhythmias [18], ventricular septal rupture [19], coronary spasm [20], ischemia and acute coronary syndromes [21] are the defined clinical presentations associated with myocardial bridge. Its prevalence varies from 1.5% to 16% in angiography series and as high as 80% in autopsy series [22, 23]. In our study the prevalence of myocardial bridge was 2.16% (n=35, study population=1617) which accounts for 47.94% (n=35, patients with CAAs=73) of CAAs. Our data is compatible with the literature. Myocardial bridge, previously seen as an harmless anatomic variant of the coronary artery course, nowadays is believed to have fatal consequences. However, the exact mechanism for this is yet to be clarified. Several pathophysiological explanations have been suggested: i). Most of the myocardial perfusion occurs during diastole (with estimated 85% of blood flow) and less during systole (with estimated 15% of blood flow). Since myocardial bridge is a systolic compromise in nature, one can consider that is not a significant factor to induce ischemia. However, when the heartbeats accelerate (in tachycardia states), systolic blood flow gains importance due to shortened diastolic filling time [24] and decreased coronary flow reserve (a measure of the ability to augment coronary blood flow under stress) [25]. ii). Kinking of the coronary arteries during tachycardia may cause endothelial damage due to continuous trauma in turn ending with platelet aggregation, vasospasm and acute coronary syndromes [26]. iii). Moderate-to-high laminar shear stress is the most important survival factor for endothelial cells to produce and release NO (nitric oxide). Due to distorted normal laminar blood flow pattern, NO production and bioavailability decrease and the coronary artery is exposed to ET-1 (endothelin-1) effect with a reduction or complete loss of NO to counteract it [27]. After all, myocardial bridge leads interstitial fibrosis, replacement fibrosis, contraction band necrosis, increased vascular density in the affected area and leads to variable clinical conditions.

**Separate origin of LAD and CX from the left sinus of Valsalva (absent left main trunk) (Figure 1: C-D).**

One of the milestone studies about incidence and characteristics of CAAs was conducted by Yamanaka O and Hobbs RE 1990 [10]. They identified 1686 (1.3%) CAAs in a total of 126,595 patients who underwent coronary angiography at the Cleveland Clinic Foundation from 1960 to 1988. Separate origin of LAD and CX from the left SoV was the most seen anomaly with an incidence of 0.41% (n=513, study population=126,595). LAD and CX arise from separate ostia but adjacent from left SoV and their course and distribution are normal otherwise. This anomaly is benign in nature and has no hemodynamics compromise. Cannulation of the ostia during conventional coronary angiography may be difficult or even impossible in some patients; that could be misinterpreted as total obstruction or congenital absence of the vessels. Absence of LMCA trunk or
Coronary artery fistulas (Figure 2: A).
Coronary artery fistulas (CAFs), termination anomalies of coronary arteries, are abnormal connections between coronary arteries and any other structures. The incidence of CAFs was 0.18% (n=225, study population=126,595) and 13% (n=225, CAAs=513) as a proportion of CAAs in the study conducted by Yamanaka O and Hobbs RE [10]. Most of the CAFs arise from the LAD and RCA and drain off to right ventricle, right atrium, coronary sinus, pulmonary artery, left atrium and left ventricle. Myocardial ischemia, coronary steal, pulmonary arterial hypertension, congestive heart failure, bacterial endocarditis, and even rupture are among the presentations of CAFs. CAFs are the third most commonly seen anomalies in our study with a prevalence of 0.61% (n=10, study population=1617), accounting for 13.69% (n=10, patients with CAAs=73) of CAAs. In our study, CAFs are one of the most commonly seen anomalies, compatible with the current literature in relation to anomalous origin of CX arising from right SoV.

Origin of RCA from left sinus of Valsalva (Figure 2: C).
Anomalous origin of RCA from left SoV is suspected when selective coronary angiography of RCA is unable to be performed from the right SoV. In this anomaly RCA originates from an orifice located anterior to the LMCA. It is very hard to cannulate this anomaly during selective coronary angiography due to its orifice and angulation. It arises from the left SoV and passes through the pulmonary artery and aorta. Angina pectoris, myocardial infarction, ventricular tachycardia, syncope, and sudden death can result from this anomaly even in the absence of coronary atherosclerosis. Yamanaka O and Hobbs RE [10] reported its prevalence as 0.107% (n=136, study population=126,595) in their study. We have a prevalence of 0.12% (n=2, study population=1617) in our present study. Altin et al. presented an incidence of 0.072% of anomalous origin of RCA from left SoV in studies from our country [29]. Our data is compatible with the current literature.

Origin of CX from right sinus of Valsalva (Figure 2: B).
In this anomaly CX arises from the right SoV, courses posterior to the aorta, and provides branches to the left lateral wall of the heart. It is a quite common anomaly. Yamanaka O and Hobbs RE [10] reported an incidence of 0.37% (n=467, study population=126,595) as the second most commonly seen anomaly in their study. It is thought to be benign. It can be suspected when there is absent LMCA with LAD origination alone from the left SoV and nonperfused left lateral wall. It can be visualized by chance while trying to cannulate RCA. It can lead to increased radiation exposure to the operator or misinterpreted to be occluded during diagnostic procedures. It should be carefully reported in the patient’s data and the surgeon must be alerted in case of cardiac surgeries as for all the other CAAs. We define three patients out of 1617 patients with this anomaly, for a prevalence of 0.18%. Ten patients were identified to have anomalous origin of CX arising from right SoV out of 5548 patients who underwent coronary angiography, for a prevalence of 0.18% in a study conducted in our country [29]. Our data is compatible with the current literature in relation to anomalous origin of CX arising from right SoV.

Absent Obtus Marginalis (OM)
There were no publications about absent OM in the literature. We came across this anomaly in two patients in our series. Diagonal branches of LAD supplied blood flow to the absent OMs’ area in these patients. The prevalence of the anomaly is 0.12% (n=2, study population=1617). To the best of our knowledge, ours is the first study to note the presence of this anomaly.

Woven coronary anomaly
Woven coronary anomaly, poorly understood to date, is division of an epicardial coronary artery into small branches: twisting of these small branches around their structure and merging again distally to form same coronary artery to supply myocardium. Transverse cut view of the vessel shows multiple small vessels in the area. Distal blood flow rate is generally preserved but may be compromised in some patients. Woven coronary anomaly is generally considered a benign anomaly. However, coronary artery dissection, thrombus formation and chronic total occlusion of artery with bridging collaterals could be confused as an alternative diagnosis and further unnecessary intervention could be performed. The incidence of the anomaly is not known. There are 23 adult cases published in the literature. RCA is the most affected artery followed by LAD and CX in this report [30]. The prevalence of this anomaly is 0.12% (n=2, study population=1617).
This anomaly is extremely rare. RCA arising from posterior sinus of Valsalva slightly higher than in previously published studies. Our prevalence was a prevalence of 0.061%. This anomaly was reported to have a prevalence of 0.02% to 0.04% in coronary angiography series. We identified one patient with single coronary artery arising from left SoV with a prevalence of 0.061% (n=1, study population=1617).

Dual LAD (Figure 3: B).
The presence of two coronary arteries in the anterior interventricular groove is identified as dual LAD. In this anomaly two vessels supply the septum and anterior wall of the left ventricle. Six subtypes of this anomaly are defined so far. In the first three forms the short and the long LADs arise from the LMCA. A short LAD originates from the LMCA and a long LAD from RCA in the fourth subtype. In the fifth subtype, the short LAD arises from the left SoV and the long LAD arises from the right SoV with an intramyocardial course. In the sixth subtype, the short LAD arises from the LMCA and the long one from the RCA with a course underneath right ventricular outflow tract. The anomaly is generally thought to be benign. The prevalence of the disease was reported to be 0.041% in 12,059 patients undergoing coronary angiography from the western side of Turkey [7]. We defined one patient with dual LAD with prevalence of 0.061% (n=1, study population=1617). In our patient both the short and the long LAD arose from the LMCA.

Figure 3. Coronary angiography image of single coronary artery (A). Coronary angiography image of dual LAD (B).

Coronary artery crossing
It is assumed that coronary arteries course parallel to each other and do not cross each other. It is a very rare anomaly and believed to be benign [35]. Despite coronary artery crossing being found usually in OM branches of CX, it can be found in LAD and RCA also. We defined one patient with coronary artery crossing in OM with a prevalence of 0.061% (n=1, study population=1617).

Selection of the patients to the study is the major limitation of our study as previously stated in the literature. The real world incidence of CAAs could not be determined properly because of the limited number of patients and biased inclusion criteria. Also, the fact that patients underwent coronary angiography can distort the incidence and prevalence because of their high probability of having coronary artery disease, ischemia and symptoms. The definition of CAAs varies from study to study (e.g., myocardial bridge is not accepted as a CAA in one of the milestone studies of CAA conducted by Yamanaka et al. with 126,595 patients). We are a tertiary center university hospital and we perform angiographies through femoral access site due to failure of radial access site or other issues. This can also be
a limitation to our study. Due to ethical concerns, the CAA di-
agnoses could not be confirmed with other imaging modalities
(radiation exposure, lack of MRI angiography).

To date, there was no data concerning the prevalence of CAAs in the Black Sea Region. This is the first study performed in this area and the second one that showed the feasibility and safety of trans radial access in diagnosis of CAA. The incidence of CAA ranges from study to study according to definitions and geo-
graphical location. Some of the CAAs may be related to angio-
mal symptoms, myocardial infarction, and sudden death despite generally being in benign nature. To avoid misunderstandings one must know the normal anatomy of coronary vasculature, variations and anomalies. When coronary angioplasty or car-
diac surgery is planned in patients with CAA, special attention must be paid not to harm coronary arteries in unexpected loca-

Scientific Responsibility Statement

The authors declare that they are responsible for the article’s scientific content including study design, data collection, analy-

sis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and ap-

proval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national re-
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Conflict of interest

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