Critical Observations on the Dynamic Change in Caliber of Interarterial Segment of Anomalous Coronary Arteries on CT Angiogram in Patients with Chest Pain and Treadmill Test Findings - A Potential ‘Game-Changer’ Information in the Patient Management

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Research Article

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Abstract

Aims and background

The incidence of coronary artery anomalies is rare in the general population, anomalous origin of right coronary artery being the most common. These anomalies, particularly anomalous coronary arteries with an interarterial course (ACAIAC) are potentially dangerous. Due to their low incidence, meticulous clinical and imaging guidelines have not yet been defined in assessing such patients and guiding management.

Methods and results

CT coronary angiograms of patients who underwent the study for exclusion of coronary artery disease were reviewed. Patients with ACAIAC were recorded. The images were reviewed and reconstructed to measure the caliber and area of the narrowest interarterial segment of ACAIAC in systolic and diastolic phases using Philips Intellispace version 12.1 software.

Percentage change in area (p value 0.093) and diameter (p value 0.108) of the interarterial segment in systolic and diastolic segments, was statistically significant between anomalous coronaries with high and low interarterial course. Percentage change in area and diameter between patients with positive and negative TMT findings was also statistically significant (p<0.001 in both cases).

Conclusion

Significant positive correlation between change in vessel caliber in the interarterial course of coronary arteries during the cardiac cycle and TMT findings, suggests elevated risk of inducible ischemia in patients with significant vessel compression. Hence the change in vessel caliber can be used as a potential criterion for risk assessment and management of patients with ACAIAC.

Introduction

Incidence of anomalous aortic origin of the coronary arteries have been reported in 0.14-1.74% of the population according to various studies.[1] The course of the anomalous vessel may be intramural, interarterial, intramyocardial, pre-pulmonic, subpulmonic or retro-aortic. The interarterial course or ‘malignant’ course of the artery has been predicted to be a risk factor of sudden cardiac death (SCD) in young athletes. [2, 3] Anomalous coronaries have been known to cause various symptoms like dyspnea on exertion, palpitations, arrhythmias and even sudden cardiac death. However, patients can also be entirely asymptomatic. [3, 4] The patho-physiology of restricted coronary blood flow seen in interarterial courses have been suggested to be the acute takeoff angle, the slit-like ostium, the compression of the intramural segment by the aortic valve commissure and the compression of the artery between the aorta and the main pulmonary artery.[5]

Anomalous origin of the right coronary artery (RCA) from the left coronary sinus (AORL) has been reported to be more common compared to anomalous origin of left coronary artery.[6,7 and 8] The
hemodynamic significance of AORL with an interarterial course (IAC) differs according to the location of the anomalous RCA ostium, because the hemodynamic significance might depend on the degree of RCA ostium compression and/or the interarterial RCA segment. Accordingly, RCA ostium located above the pulmonary valve is termed “high interarterial course (HIC)” and an RCA ostium below the pulmonary valve is termed “low interarterial course (LIC)”. The RCA segment between the two great vessels (HIC), the aorta and main pulmonary artery would be more likely to be compressed during systole, as blood is forced into these vessels, compared to LIC.[5]

Oblong or slit like lumen has also been suggested to carry a higher risk of SCD in cases of IAC.[9] An acute angle takeoff of a coronary artery, namely, angle between the proximal coronary artery and the aortic wall of less than 45°, may further compress the coronary artery at its point of takeoff which may lead to SCD.[10] While many risk factors are proposed, present CT angiograms can demonstrate some of the risk factors in static and dynamic phases, making observations relevant in clinical decision making.

**Material And Methods**

**Study design**

An observational descriptive study, was carried out at the Radiology Department of Narayana Hrudyalaya, Bangalore during the period of June 2016 to May 2018. Study was approved by the Ethics Committee and Medical Research Department. We reviewed CT coronary angiography data of patients who underwent the procedure as a screening or rule out coronary artery disease.

Objectives of the study were to study the prevalence of inter arterial / malignant course of coronary arteries; to study the variations in the IAC of anomalous coronary arteries and to find the association between change in vessel calibers in systolic & diastolic phases at the IAC of anomalous coronary arteries and correlate changes with chest pain and results of treadmill test. Suboptimal exams wherein systolic and diastolic measurements could not be performed were excluded. Patients with occluded or severely diseased coronary arteries with CAD RADS score >2, were also excluded.

**Patient preparation and study protocol:**

Patients were pre-medicated with Tab. Metaprolol orally or Tab. Diltiazem (in asthmatics) or Tab. Ivabradine along with Tab. Alprazolam 0.25 mg to maintain heart rate between 60-70 bpm and to reduce anxiety. Scans were performed using 128 slice multidetector Philips Ingenuity 128 slice CT scanner (Koninklijke Philips N.V) and a dual flow injector. Retrospective ECG triggering was used. Iohexol (Omnipaque 350 mg/ml) was injected in the dose of 1-1.5 ml/kg and flow rate of 5.5 ml/sec followed by saline chase. Bolus track method was used for triggering with ROI at ascending aorta and threshold of 120 HU. Images were reconstructed with slice thickness of 0.6-0.7 mm. Images were reconstructed on a workstation (Philips workstation with Intellispace Ver 12.1 software) to generate images in multiple phases, 3D (volume rendering) and curved planar reconstruction (CPR). Technical parameter of CT angiography is provided in Table1. The caliber and area of the narrowest interarterial segment of
anomalous coronary artery was measured in systolic and diastolic phases using Philips Intellispace version 7 software

**Statistical analysis:**

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test or Fischer’s exact test (for 2x2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and SD. Independent ‘t’ test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

**Results**

We reviewed the CT angiograms of 6299 patients. The prevalence of IAC of coronary artery abnormality was seen in 0.77% (49 patients). We excluded 13 patients with CAD-RADS score of 2 or more, left with 36 patients for analysis. In our study, we recorded observations in patients with anatomical variations of interarterial course (subtypes of IAC, slit like course and acute angle takeoff) with chest pain and TMT findings separately. The results of the study are described below.

The mean age of this group was 50.18 ±11.15 years with 72.2% of patients being male. 35 patients (97.2%) had AORL with an interarterial course and 1 patient (2.8%) had LMCA arising from the right anterior sinus with AC. In AORL, 22 patients (62.8%) had HIC and 13 patients (37.2%) had LIC. The single case of LMCA originating from right anterior sinus had LIC. In patients with HIC, acute angulation at the origin was present in 100% (22 patients) and slit-like course was present in 77.3% (17 of 22 patients). In patients with LIC, acute angulation at the origin was present in 85.7% (12 of 14 patients) and slit-like course was present in 28.6% (4 of 14 patients). There was a statistically significant difference in slit-like course distribution between two groups (p value 0.004) and there was no significant difference in acute angle takeoff at the origin distribution between two groups (p value 0.068).

In patients with HIC, chest pain was present in 68.2% (15 of 22 patients) and TMT was positive in 45.5% (10 of 22 patients). In patients with LIC, chest pain was present in 64.3% (9 of 14 patients) and TMT was positive in 14.3% (2 of 14 patients). There was no significant difference in occurrence of chest pain (p value 0.809) and TMT findings between two groups (p value 0.053).

In HIC, mean systolic area and diameter was 5.236 ± 1.369 mm$^2$ and 1.500 ± 0.495 mm respectively. In LIC, mean systolic area and diameter was 7.629 ± 3.879 mm$^2$ and 2.171 ± 0.897 mm respectively. This difference in systolic area (p value 0.012) and diameter (p value 0.007) between high and low group was statistically significant.
The mean diastolic area was $6.873 \pm 1.516 \text{ mm}^2$ and mean diastolic diameter was $1.995 \pm 0.509 \text{ mm}$ in patients with HIC. The mean diastolic area was $8.500 \pm 4.017 \text{ mm}^2$ and mean diastolic diameter was $2.379 \pm 0.885 \text{ mm}$ in patients with LIC. This difference in diastolic area (p value 0.093) and diameter (p value 0.108) between high and low group was not statistically significant.

In HIC, percentage change in mean area and diameter was $23.692 \pm 14.962\%$ and $24.706 \pm 14.276\%$ respectively. In LIC, percentage change in mean area and diameter was $11.007 \pm 9.306\%$ and $9.632 \pm 7.794\%$ respectively. This difference in percentage change in area (p value 0.008) and diameter (p value 0.001) between HIC and LIC was statistically significant.

In patients with positive TMT, slit like course was present in 83.3% and among those with negative TMT 45.8% had slit like course. This difference was statistically significant (p value 0.031). However, no association was found between TMT results and angulation at the AORL origin.

Among those with positive TMT, the mean systolic area was seen to be $5.4 \text{ mm}^2$, mean systolic diameter 1.5 mm, mean diastolic area $7.7 \text{ mm}^2$ and mean diastolic diameter 2.1 mm. Whereas in TMT negative patients mean systolic area was seen to $6.4 \text{ mm}^2$, mean systolic diameter 1.8 mm, mean diastolic area $7.3 \text{ mm}^2$ and mean diastolic diameter 2.1 mm.

The percentage change in mean area was $29.800 \pm 13.852\%$ in those with positive TMT, and in those with negative TMT percentage change in mean area was $13.239 \pm 11.226\%$. This difference in percentage change in area between those with positive and negative TMT findings was statistically significant (p value <0.001).

In patients with positive TMT, percentage change in mean diameter was $30.605 \pm 13.301\%$ and in those with negative TMT percentage change in mean diameter was $12.964 \pm 10.586\%$. This difference in percentage change in diameter between those with positive and negative TMT findings was statistically significant (p value <0.001).

**Discussion**

To our knowledge, this is a unique study relating to the measurement of change in vessel caliber in anomalous coronaries during the cardiac cycle. We did not come across studies with similar intent and exploration in the literature. Anomalous coronary arteries have been reported to cause various cardiac symptoms and mechanisms have been hypothesized as to the pathophysiology. Physical exertion in such individuals can lead to accentuation of precarious hemodynamics leading to restricted myocardial blood flow, even myocardial ischemia and sudden death. [11–14] However, some patients with this entity may remain entirely asymptomatic. It is imperative to identify the patients at risk of potential myocardial ischemia, as surgical intervention is beneficial only in such cases. [15–17] In this study we have assessed the anomalous location of ostium of coronary vessels, the variation in the systolic and diastolic diameter and area of their interarterial segments to identify individuals at risk of myocardial ischemia.
Since slit-like ostium and acute angle at take-off were more frequently seen in patients with high take off anomalous coronary artery, these anatomical configurations may be assumed to be the indicator for higher risk. However, the occurrence of chest pain and positive TMT findings did not show statistically significant differences between the two groups.

The significant percentage change in mean area and diameter of the artery between cases of HIC and LIC concurs with the hypothesis by Lee et al, which proposes that hemodynamic significance of AORL with an interarterial course differs according to the location of the anomalous RCA ostium due to greater compression of the interarterial segment of anomalous coronaries with high origin.\[5\] However, HIC and LIC did not show significant correlation with TMT findings. Additionally, significant positive correlation was seen between change in vessel caliber in the interarterial course of coronary arteries in the cardiac cycle and positive TMT findings. This points to an important fact that anatomical classification into HIC and LIC doesn’t adequately categorize the ischemic risk, but the absolute percentage of compression does. Therefore, it is imperative to assume that it is not only the type of IAC, but also the degree of compression that should be taken into consideration when predicting risk assessment, thus, guide the decision on the management strategies in patients with interarterial coursing of coronaries.

Specific anatomic characteristics of patients with IAC of coronary arteries on CT coronary angiogram and relation between major adverse cardiac events have been studied earlier to distinguish patients at risk of adverse events.\[16, 18\] However, there are no relevant literature on the assessment of change in vessel caliber during the cardiac cycle in patients with IAC of coronary arteries and clinical significance. Hence, we believe that results of our study bridge the earlier lacunae, providing a more comprehensive basis for the patient management. This element of information should be carefully explored while deciding the treatment of anomalous coronary artery arising from the opposite sinus.

Ashrafpoor et al. assessed in their study, the relation between major adverse cardiac events and anatomical criteria determined by coronary computed tomography angiography. A significantly smaller minimal lumen area was seen in patients with adverse coronary events (3.6 mm\(^2\) vs 9.0 mm\(^2\)).\[18\] In our study, the difference in minimal lumen area (systolic phase lumen) was not significant (5.4 mm\(^2\) vs 7.4 mm\(^2\)). In fact, only three patients in our study had a minimal lumen area ≤3.6 mm\(^2\), one had negative TMT, second had positive TMT (borderline symptoms) and the third had a positive TMT (symptomatic, minimal lumen area of 1.7mm\(^2\) and area difference of 55% and 35% change in diameter), He underwent reinsertion of the anomalous RCA onto right coronary cusp and improved clinically. Hence, we are of the opinion that an absolute single measurement of the interarterial segment as suggested in earlier study, does not provide adequate assessment.

Many studies have assessed the anatomic parameters of ACAIAC particularly in young patients. Study by Lee et al comparing the “high-risk” morphologic characteristics of anomalous aortic origins of RCA vs left coronary artery showed no significant differences with respect to any morphologic features between the symptomatic and asymptomatic patients with ACIAC.\[19\] To prognosticate future adverse cardiac events,
we need to look at factors which places them at higher risk. Adding dynamic coronary imaging in the CCA protocol is first step towards this direction.

Though traditionally believed that slit like course and ostial angulation were significant risk factors in SCD, our study did not show positive correlation of ostial angulation with positive stress testing. Similar observations were made in the study by Palmieri et al. [20] We also found a higher correlation of percentage change in caliber with stress testing results. Though we could not arrive at an absolute cut-off that would serve as a deciding factor in choosing management options, higher percentage of change in caliber in symptomatic individuals, along with anatomical factors could be added in establishing risk factor in SCD.

The positive TMT findings in patients with significant change in vessel caliber is an indication that the increased ventricular output during exertion, adds to vascular compromise, leading to increased risk of myocardial ischemia and SCD. As surgery is currently indicated only in symptomatic patients, identifying the patients who would benefit from surgery in a timely manner is critical to the management.[15, 16]

There is also great variability in the existing guidelines for treatment of ACIAC in asymptomatic patients with wide ranging recommendations – from global recommendation of surgical repair in all teenagers to a very small subset of patients with defined criteria requiring intervention.[21–24] Though exercise testing is routinely performed in ACIAC, an positive exercise test does not provide significant reassurance. Adverse cardiac events occur even in previously asymptomatic patients as well.[25] It is imperative that we follow-up cases of borderline risk, and equally important to reassure patents in low risk or no increased risk regarding their management strategy. Risk stratification thus seems essential to the management. We hope that including criterion of dynamic assessment of interarterial segment caliber offer much needed information in solving the management dilemma.

**Conclusion**

The dynamic assessment of change in coronary arterial caliber during cardiac cycle in patients with IAC of coronary arteries is a novel concept in the management evaluation of anomalous coronary arteries. Percentage change in vessel caliber is a potential criterion that can be used in risk assessment for coronary ischemia when considering medical and interventional management in anomalous coronary arteries with an IAC. Inclusion of dynamic study protocols are likely to provide more predictable outcome parameters for patient selection for definitive procedures. Further exploration of the concept, validation of observations and defining the objective cut-off values of significance for patient management are highly desirable.

**Declarations**

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Tables

Table 1
Coronary CTA scan parameters

| Scan area                  | From ascending aorta to diaphragm |
|----------------------------|-----------------------------------|
| Scan length                | ~12.5 cm                          |
| Scan direction             | Cranio-caudal                      |
| Tube voltage               | 120 kV                            |
| Tube current               | 900 mAs                           |
| CTDIvol (average)          | ~59 mGy                           |
| DLP (average)              | ~1000 mGy*cm                      |
| Rotation time              | 0.4 sec                           |
| Detector coverage          | 40 mm                             |
| Slice width                | 3 mm                              |
| Pitch                      | 0.2 – 0.3                         |
| Recon. increment           | 0.67 mm                           |
| Window setting             | Window width = 750, Window Level = 90 |
| Matrix Size                | 512 x 512                         |
| Contrast (Omnipaque 350 mg / mL) | 1.0 – 1.5 mL / kg + 20-30 mL of saline chase |
| Contrast flow rate         | 5.5 mL / s                        |
| Trigger                    | Bolus tracking                     |
| Post threshold delay       | 5 sec                             |
Table 2
Area and diameter comparison of interarterial segment between patients with and without chest pain

|                      | Chest pain |        |        | P value |
|----------------------|------------|--------|--------|---------|
|                      |            | Yes    | No     |         |
|                      |            | Mean   | SD     | Mean    | SD      |
| Systolic             |            |        |        |         |
| Area                 |            | 6.279  | 2.825  | 5.942   | 3.006   | 0.743 |
| Diameter             |            | 1.842  | 0.778  | 1.600   | 0.680   | 0.367 |
| Diastolic            |            |        |        |         |
| Area                 |            | 7.788  | 2.800  | 6.942   | 2.933   | 0.406 |
| Diameter             |            | 2.271  | 0.730  | 1.892   | 0.563   | 0.124 |
| Percentage change in |            |        |        |         |
| caliber              |            |        |        |         |
| Area difference      |            | 20.587 | 15.807 | 15.103  | 10.514  | 0.097 |
| Diameter difference  |            | 19.870 | 14.398 | 16.793  | 14.044  | 0.546 |

Table 3
Area and diameter comparison of interarterial segment between patients with positive and negative TMT findings

|                      | TMT          |        |        | P value |
|----------------------|--------------|--------|--------|---------|
|                      |              | Positive | Negative |         |
|                      |              | Mean    | SD     | Mean    | SD      |
| Systolic             |              |        |        |         |
| Area                 |              | 5.542   | 1.812  | 6.479   | 3.235   | 0.359 |
| Diameter             |              | 1.542   | 0.623  | 1.871   | 0.789   | 0.217 |
| Diastolic            |              |        |        |         |
| Area                 |              | 7.758   | 1.921  | 7.379   | 3.223   | 0.711 |
| Diameter             |              | 2.192   | 0.601  | 2.121   | 0.748   | 0.778 |
| Percentage change in |              |        |        |         |
| caliber              |              |        |        |         |
| Area difference      |              | 29.800  | 13.852 | 13.239  | 11.226  | <0.001* |
| Diameter difference  |              | 30.605  | 13.301 | 12.964  | 10.586  | <0.001* |
Table 4
Association between various parameters with TMT

| Parameter                              | TMT |   |   |   |   | P value |
|----------------------------------------|-----|---|---|---|---|---------|
|                                        | TMT |   |   |   |   |         |
|                                        |     | Count | Percentage | Count | Percentage |         |
| Coronary artery Origin                 |     | Positive | 0 | 0.0% | 1 | 100.0% | 0.473 |
|                                        |     | Negative | 0 | 0.0% | 1 | 100.0% |         |
|                                        |     | LMCA from right coronary cusp | 0 | 0.0% | 1 | 100.0% | 0.473 |
|                                        |     | RCA from left coronary cusp | 12 | 34.3% | 23 | 65.7% |         |
| Acute angulation at the origin         | Yes | 12 | 35.3% | 22 | 64.7% | 0.303 |
|                                        | No  | 0  | 0.0%  | 2  | 100.0% | 0.303 |
| Slit-like orifice                      | Yes | 10 | 47.6% | 11 | 52.4% | 0.031* |
|                                        | No  | 2  | 13.3% | 13 | 86.7% |         |

Figures
CT coronary angiography MPR image of 48 years old male with history of chest pain and negative TMT, showing systolic (c,d) (Area – 16.2 mm\(^2\); Diameter – 4.0 mm) and diastolic (a,b) (Area – 18.2 mm\(^2\); Diameter – 4.3 mm) phases of low interarterial course of RCA without significant change in caliber during cardiac cycle.
Figure 2

CT coronary angiography MPR image of 38 years old male with history of chest pain and positive TMT, showing systolic (c,d) (Area – 5.5 mm$^2$; Diameter – 1.6 mm) and diastolic (a,b) (Area – 7.5 mm$^2$; Diameter – 2.3 mm) phases of high interarterial course of RCA with significant change in caliber during cardiac cycle.