



Evaluation of the Ostium in Anomalous Origin of the Right Coronary Artery with an Interarterial Course Using Dynamic Cardiac CT and Implications of Ostial Findings

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Objective: We aimed to evaluate the ostium of right coronary artery of anomalous origin from the left coronary sinus (AORL) with an interarterial course throughout the cardiac cycle on CT and analyze the clinical significance of the ostial findings.

Materials and Methods: From January 2011 to December 2015, 68 patients (41 male, 57.3 ± 12.1 years) with AORL with an interarterial course and retrospective cardiac CT data were included. AORL was classified as high or low ostial location based on the pulmonary annulus in the diastolic and systolic phases on cardiac CT. In addition, the height, width, height/width ratio, area, and angle of the ostium were measured in both cardiac phases. After cardiac CT, patients were followed until December 31, 2020 for major adverse cardiac events (MACE). Clinical and CT characteristics associated with MACE were explored using Cox regression analysis.

Results: During a median follow-up period of 2071 days (interquartile range, 1180.5–2747.3 days), 13 patients experienced MACE (19.1%, 13/68). Seven (10.3%, 7/68) had the ostial location change from high in the diastolic phase to low in the systolic phase. In the univariable analysis, younger age (hazard ratio [HR] = 0.918, $p < 0.001$), high ostial location (HR = 4.008, $p = 0.036$), larger height/width ratio (HR = 5.621, $p = 0.049$), and smaller ostial angle (HR = 0.846, $p = 0.048$) in the systolic phase were significant predictors of MACE. In multivariable cox regression analysis, younger age (adjusted HR = 0.917, $p = 0.002$) and high ostial location in the systolic phase (adjusted HR = 4.345, $p = 0.026$) were independent predictors of MACE.

Conclusion: The ostial location of AORL with an interarterial course can change during the cardiac cycle, and high ostial location in the systolic phase was an independent predictor of MACE.

Keywords: Coronary vessel anomaly; Coronary computed tomography angiography; Cardiac computed tomography; Retrospective gating

INTRODUCTION

Anomalous origin of the right coronary artery (RCA) from the left coronary sinus (AORL) with an interarterial course has been associated with myocardial ischemia, which is in turn related to arrhythmia, myocardial infarction (MI), and sudden cardiac death [1]. The reported prevalence of

this anomaly is approximately 0.23%, and it is a common coronary anomalies observed on cardiac CT [2]. However, as experience with this anomaly accumulates due to the widespread use of cardiac CT, we have found that AORL with an interarterial course does not necessarily lead to serious cardiovascular events [3]. Hence, much research has been done on risk stratification and optimal management of the

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anomaly, especially based on cardiac CT findings. Thus far, potentially dangerous AORL with an interarterial course seems to have the following anatomical criteria: an acute take-off angle, minimum luminal area, slit-like ostium, narrowing length, and proximal intramural course within the aortic wall [2,4-10]. However, no significant relationship has been observed between these anatomic variations and clinical outcomes in a prior autopsy study [11]. In contrast, another study using cardiac CT classified AORL with an interarterial course into two subtypes according to the location of the anomalous RCA ostium [12]. The high ostial location was defined as an ostial location between the aorta and pulmonary artery and the low ostial location was defined as an ostial location between the aorta and right ventricular outflow tract; the high ostial location was significantly related to major adverse cardiac events (MACE) and typical angina [12]. However, this finding has not been validated and has even been questioned because the former study was performed only using images from the best cardiac phase, regardless of the hemodynamic perspective [4].

We hypothesized that by considering cardiac motion, the location of the AORL with an interarterial course to the pulmonary artery of the anomalous RCA ostium would differ during the cardiac cycle, and the hemodynamic significance of the anomaly would vary accordingly. Furthermore, as simultaneous distention of the aorta and pulmonary artery occurs during systole when blood is forced into the great vessels, classifying the anomalous RCA ostial location relative to the pulmonary artery might have more significance in the systolic phase than the diastolic phase. Therefore, the purpose of this study was to evaluate the ostium of AORL with an interarterial course, including the high or low ostial locations, in both diastolic and systolic phases using cardiac CT and analyze the clinical significance of ostial findings with an emphasis on location.

MATERIALS AND METHODS

Study Population

Our Institutional Review Board and the Local Ethics Committee approved this retrospective study and waived the requirement for informed consent (IRB No. 4-2020-0819). After searching our database for cardiac CT examinations performed at our institution from January 2011 to December 2015, we found 18828 consecutive patients who underwent cardiac CT to evaluate coronary artery disease. Among them, we identified 141 patients

(0.7%; 141/18828) with AORL with an interarterial course. Patients with other cardiac disease, such as coronary artery disease (38 patients), other coronary artery anomalies (three patients), myocardial disease (two patients), congenital heart disease (four patients), and valvular heart disease (six patients), were excluded. Additionally, 20 patients without retrospective CT data were excluded. Finally, a total of 68 patients were enrolled (41 male and 27 female; mean age \pm standard deviation, 57.3 \pm 12.1 years, range 21–81 years).

Clinical Findings

We evaluated symptoms for each patient. In patients with chest pain, the pain was classified as typical, atypical, and non-anginal according to the American College of Cardiology–American Heart Association guidelines [13]. We recorded the presence of other symptoms, such as dyspnea, palpitation, and syncope, in patients with no chest pain. Asymptomatic patients were regarded as having no symptoms. We reviewed electronic medical records to collect all available clinical history and clinical test results, including those for resting electrocardiogram (ECG), echocardiography, cardiac stress tests (treadmill test or cardiac nuclear scan using technetium-99m sestamibi), and conventional coronary angiography. After cardiac CT, patients were followed until December 31, 2020 for MACE through electronic medical record reviews. We only included MACE that occurred after cardiac CT and did not include events before or at the time of CT. Cardiac arrest, nonfatal MI, unstable angina requiring hospitalization, surgical treatment such as coronary artery bypass graft (CABG), unroofing procedure, and neo-ostium creation were all regarded as indications of MACE.

Cardiac CT

Cardiac CT was obtained using a second-generation dual-source CT (Somatom Definition Flash; Siemens Medical Solutions). In the absence of contraindications, patients with a heart rate higher than 65 beats per minute received 50 mg of a beta-blocker (metoprolol tartrate, Betaloc; Yuhan) before examination and a 0.3-mg sublingual dose of nitroglycerin just before scanning was initiated. A bolus of 60–80 mL iopamidol (Iopamiro 370; Bracco) was injected into an antecubital vein at a flow rate of 5 mL/s, followed by 40 mL of 40% blended iopamidol with saline, and 20 mL of saline at 5 mL/s. The scan was automatically initiated 5 seconds after a threshold level of 140 Hounsfield unit was attained in the ascending aorta in bolus tracking. Scanning

parameters were as follows: retrospective ECG-gated acquisitions, 100 reference kV and 250 reference mAs with Care kV and CAREdose4D (Siemens Healthcare), ECG pulsing window in 30%–80% of the R-R interval, 512 x 512-pixel matrix, 64 x 0.6-mm slice collimation, and 0.28 seconds rotation time. Scans were obtained from the tracheal bifurcation to the diaphragm. The field of view was adjusted according to heart size. From the scan, 10 axial-image data sets were reconstructed for each 10% of the cardiac cycle using a slice thickness of 0.75 mm, increment interval of 0.5 mm, and medium-smooth convolution kernel of iterative reconstruction (I36f).

Image Analysis

Two observers (10 and 12 years of experience in cardiac imaging, respectively) who were blinded to each patient's clinical findings initially reviewed CT images independently, and then reached a consensus on the CT findings. All cardiac CT images were transferred to a software system (Aquarius iNtuition, Ver 4.4.11, TeraRecon) for analysis. In addition to the axial images, cardiac CT images were reformatted to coronal, sagittal, aortic valve view with its perpendicular view, and volume-rendered images for analysis.

AORL with an interarterial course was evaluated in both the diastolic (70%–80% of the cardiac cycle) and systolic phase (30%). Anomalous RCA ostium was divided into two subtypes according to its location in reference to the adjacent pulmonary valve annulus. If the ostium originated from the aorta above the level of the pulmonary valve

annulus, the anomaly was classified as having a high ostial location. If the ostium was located below the annulus, i.e., right ventricular outflow tract, the anomaly was classified as having a low ostial location (Fig. 1) [12]. Additionally, observers measured the ostial size by assessing height and width on the aortic valve and its perpendicular view during both diastolic and systolic phases, and calculated the area and height/width (H/W) ratio of the ostium from these values. The ostial angle was defined as the angle between the plane formed by the ostium center to a point 5 mm along the vessel centerline, and a plane tangent to the aorta in the aortic valve view during both the diastolic and systolic phases [5].

Statistical Analysis

All statistical analyses were performed using commercially available statistical software (SPSS, version 25.0; IBM SPSS Statistics, and R program, version 4.0.3.; R Foundation for Statistical Computing). Interobserver agreements regarding CT characteristics analyzed were determined through κ statistics using a contingency table for categorical variables and intraclass correlation coefficient (ICC) for continuous variables. The agreements were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement [14]. The consensus results were used for the main study analyses. The Cox regression analysis was used to estimate the association of a given variable with the occurrence

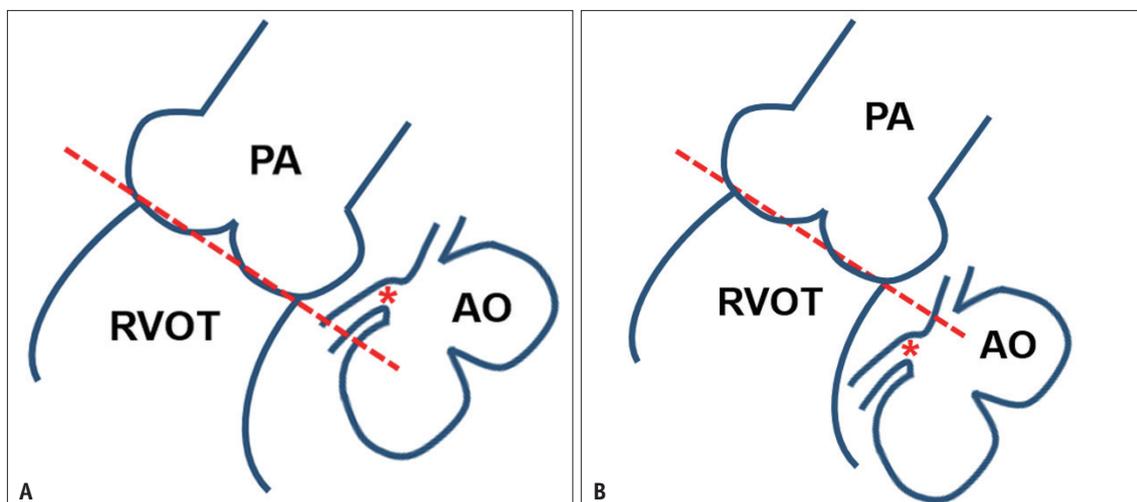


Fig. 1. Classification of ostial location.

A. The ostium (asterisk) originates from the AO above the pulmonary valve annulus (dotted line) in the high ostial location. **B.** The ostium (asterisk) is located below the pulmonary valve annulus (dotted line) in the low ostial location. AO = aorta, PA = pulmonary artery, RVOT = right ventricular outflow tract

of MACE and expressed as the hazard ratio (HR) with corresponding 95% confidence interval (CI). After testing for multicollinearity among the potential predictors of MACE using linear regression analysis, all variables with $p < 0.05$ in the univariable analysis were sequentially entered into the multivariable Cox regression analysis performed to determine independent predictors of MACE. In addition, MACE-free survival was estimated using the adjusted Kaplan–Meier method. For all data, $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Clinical Characteristics

Baseline characteristics and symptoms are summarized in Table 1. During a median follow-up period of 2071 days (interquartile range [IQR], 1180.5–2747.3 days) after cardiac CT, a total of 13 patients experienced MACE (19.1%, 13/68) with a median interval of 104 days (IQR, 27–903 days). Cardiac arrest occurred in one patient, and nonfatal MI in another; physicians could not find any other possible cause to explain their condition except a history of coronary anomaly. Unstable angina was diagnosed in seven patients, and among them, two eventually underwent surgical treatment (CABG and unroofing procedure, respectively). A total of six patients underwent surgical treatment due to recurrent symptoms. Two patients who

underwent neo-ostial creation and the unroofing procedure experienced postoperative relief of chest pain. However, two of the remaining four patients who underwent CABG still complained of chest pain despite surgical management.

CT Characteristics

The mean dose length product of cardiac CT was 318.75 ± 56.22 mGy·cm. Interobserver agreements regarding CT characteristics are summarized in Table 2. Agreement regarding ostial location was excellent in the diastolic phase ($\kappa = 0.829$) and good in the systolic phase ($\kappa = 0.786$). In addition, excellent agreement was obtained for the height, area, and angle in the diastolic phase (ICC = 0.806, 0.850, and 0.819, respectively). Good agreement was achieved for the width and H/W ratio in the diastolic phase (ICC = 0.759 and 0.651, respectively), and for the height, width, H/W ratio, area, and angle in the systolic phase (ICC = 0.796, 0.647, 0.658, 0.763, and 0.766, respectively).

The distribution of CT characteristics is summarized in Table 2. After consensus reading, the observers classified 51 patients as having a high ostial location and 17 as having a low ostial location in the diastolic phase, and 44 as having a high ostial location and 24 as having a low ostial location in the systolic phase. Seven patients had the ostial location of the AORL change from high in the diastolic phase to low in the systolic phase, but no patient had a low ostial location in the diastolic phase and high ostial location in the systolic phase (Fig. 2).

Table 1. Distribution of Clinical Characteristics of the Study Participants

	Total (n = 68)
Baseline characteristics	
Age, years	57.3 ± 12.1
Male sex	41 (60.3)
Hypertension	36 (52.9)
Diabetes	13 (19.1)
Hyperlipidemia	10 (14.7)
Current smoker	20 (29.4)
Symptoms	
Typical angina	22 (32.4)
Atypical angina	11 (16.2)
Non-anginal chest pain	8 (11.8)
No chest pain	27 (39.7)
Syncope	8 (11.8)
Dyspnea	1 (1.5)
Palpitation	6 (8.8)
No other symptoms	12 (17.6)

Data are mean ± standard deviation or patient number with percentage in parentheses.

Association between the Ostial Findings and MACE

Clinical and CT characteristics associated with MACE based on the Cox regression analysis are described in Table 3. In the univariable analysis, younger age (HR = 0.918, $p < 0.001$), high ostial location in the systolic phase (HR = 4.008, $p = 0.036$), larger H/W ratio (HR = 5.621, $p = 0.049$) in the systolic phase, and smaller ostial angle in the systolic phase (HR = 0.846, $p = 0.048$) were significant predictors of MACE. However, CT characteristics in the diastolic phase were not significant predictors of MACE. No multicollinearity was confirmed among predictors (variance inflation factor < 1.1 for all). In multivariable cox regression analysis, younger age (adjusted HR = 0.917, $p = 0.002$) and high ostial location in the systolic phase (adjusted HR = 4.345, $p = 0.026$) were independent significant predictors of MACE (Fig. 3).

Table 2. Inter-Observer Agreements and Distribution of the CT Characteristics

	Observer 1	Observer 2	Agreements	Consensus Result
Diastole				
High*	52	54	0.829 (0.668, 0.990)	51 (75)
Low*	16	14		17 (25)
Height, mm [†]	3.0 ± 0.6	3.0 ± 0.5	0.806 (0.703, 0.876)	3.0 ± 0.5
Width, mm [†]	1.8 ± 0.2	1.8 ± 0.3	0.759 (0.637, 0.844)	1.8 ± 0.2
H/W ratio [†]	1.7 ± 0.3	1.7 ± 0.3	0.651 (0.489, 0.769)	1.7 ± 0.3
Area, mm ^{2†}	4.2 ± 1.1	4.2 ± 1.1	0.850 (0.768, 0.905)	4.2 ± 1.1
Angle, degree [†]	26.4 ± 4.3	26.6 ± 4.3	0.819 (0.722, 0.884)	26.5 ± 4.1
Systole				
High*	38	45	0.786 (0.639, 0.933)	44 (64.7)
Low*	30	23		24 (35.3)
Height, mm [†]	3.2 ± 0.5	3.2 ± 0.4	0.796 (0.690, 0.869)	3.2 ± 0.4
Width, mm [†]	1.7 ± 0.2	1.7 ± 0.2	0.647 (0.484, 0.766)	1.7 ± 0.2
H/W ratio [†]	1.9 ± 0.3	1.9 ± 0.3	0.658 (0.498, 0.774)	1.9 ± 0.3
Area, mm ^{2†}	4.3 ± 0.9	4.2 ± 0.8	0.763 (0.643, 0.847)	4.2 ± 0.8
Angle, degree [†]	24.2 ± 3.8	24.6 ± 4.0	0.766 (0.646, 0.849)	25.4 ± 3.7

*Data are patient number with percentage in parentheses and the agreement is described as kappa values with 95% confidence interval in parentheses, [†]Data from each observer are mean ± standard deviation, and the agreement is described as intraclass correlation coefficients with 95% confidence interval in parentheses. H/W ratio = height/width ratio

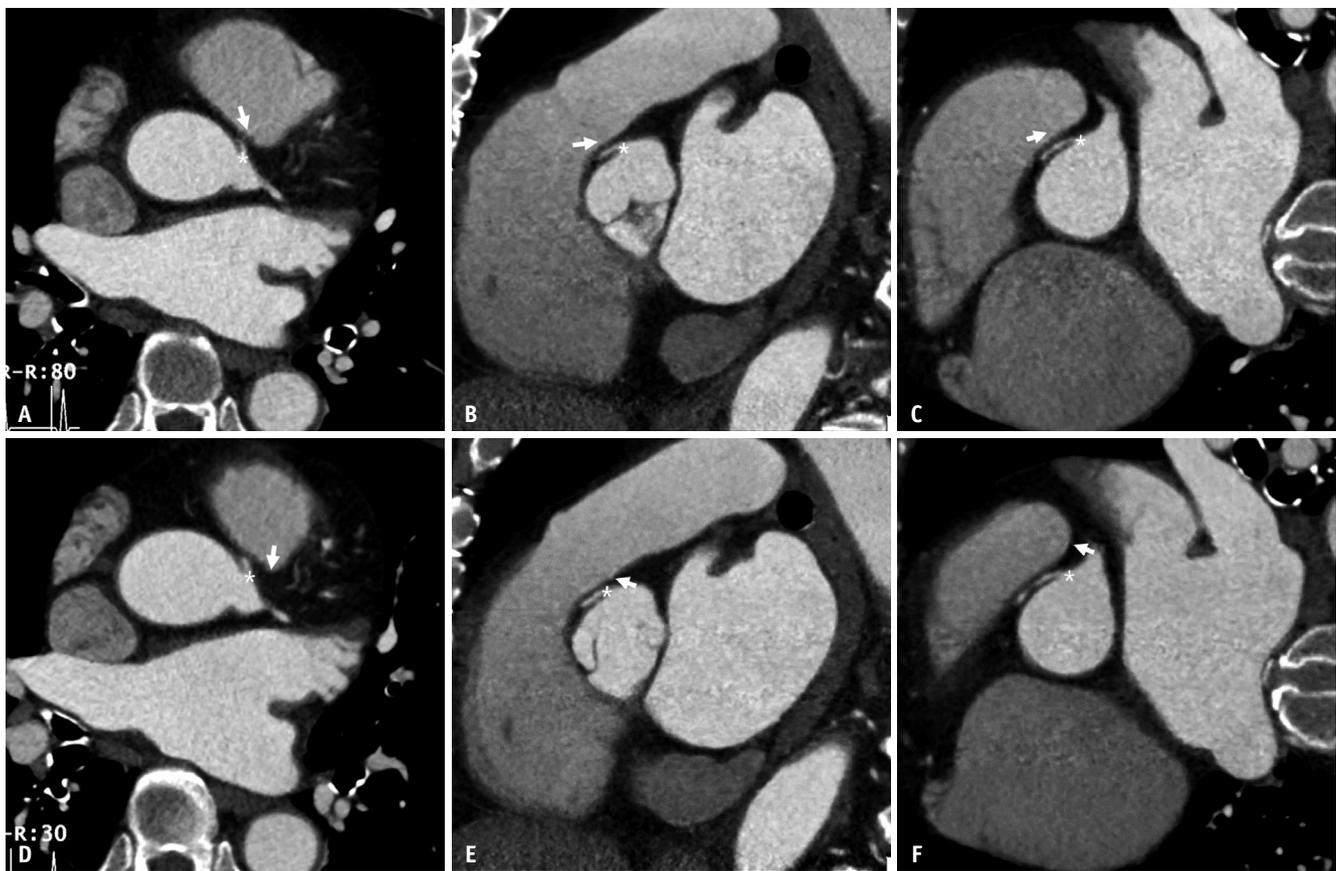


Fig. 2. Representative case of changes in ostial location occurring during the cardiac cycle.

A-C. In the diastolic phase (80% of the R-R interval), the ostium (asterisks) of the anomalous coronary artery is above the pulmonary valve annulus (arrows) on axial (**A**), sagittal (**B**), and aortic valve view (**C**) images. **D-F.** In the systolic phase (30% of the R-R interval), the ostium (asterisks) is below the pulmonary valve annulus (arrows) on axial (**D**), sagittal (**E**), and aortic valve view (**F**) images. Cardiac cine images are provided as a Supplementary movie.

Table 3. Cox Regression Analysis to Investigate Predictor of Major Adverse Cardiac Events

	Univariable			Multivariable		
	HR	95% CI	P	Adjusted HR	95% CI	P
Age, years [†]	0.918	0.878–0.960	< 0.001	0.917	0.873–0.963	0.002
Male sex (male vs. female)*	1.360	0.456–4.058	0.581	NA	NA	NA
Diastole						
Location (high vs. low)*	6.114	0.751–49.789	0.091	NA	NA	NA
Height, mm [†]	0.547	0.174–1.719	0.302	NA	NA	NA
Width, mm [†]	0.105	0.009–1.197	0.070	NA	NA	NA
H/W ratio [†]	1.612	0.268–9.686	0.602	NA	NA	NA
Area, mm ^{2†}	0.678	0.370–1.242	0.280	NA	NA	NA
Angle, degree [†]	0.889	0.776–1.041	0.153	NA	NA	NA
Systole						
Location (high vs. low)*	4.008	1.072–8.445	0.036	4.345	0.483–9.066	0.026
Height, mm [†]	1.367	0.375–4.979	0.636	NA	NA	NA
Width, mm [†]	0.064	0.004–1.061	0.055	NA	NA	NA
Area, mm ^{2†}	0.730	0.367–1.449	0.368	NA	NA	NA
H/W ratio [†]	5.621	0.998–31.661	0.049	4.193	0.647–27.165	0.133
Angle, degree [†]	0.846	0.717–0.999	0.048	0.770	0.612–0.969	0.190

*For categorical variables with categories in parentheses, the former was compared with the latter (the reference) to calculate HRs and 95% CIs with the Cox regression analysis, [†]For continuous variables with reference units in parentheses, an increase by 1 unit was considered when calculating HRs and 95% CIs with the Cox regression analysis. CI = confidence interval, HR = hazard ratio, H/W ratio = height/width ratio, NA = non-available

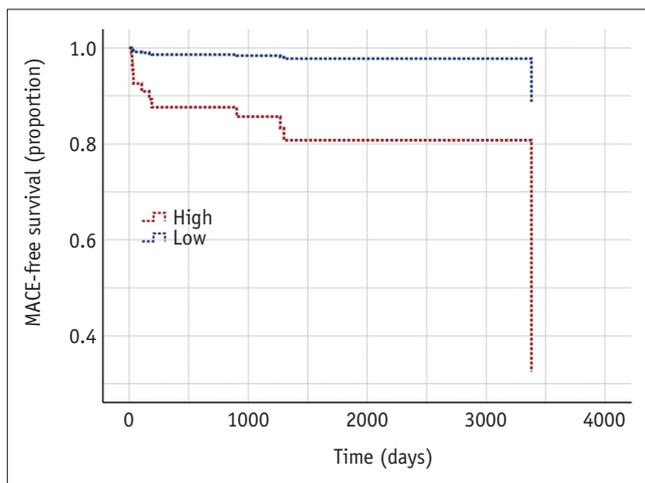


Fig. 3. Adjusted Kaplan–Meier survival curve according to the ostial location in the systolic phase. The high ostial location in the systolic phase was an independent predictor of MACE (adjusted hazard ratio = 4.345, $p = 0.026$). MACE = major adverse cardiac events

DISCUSSION

The major findings of our study were that seven patients (10.3%, 7/68) with AORL with an interarterial course showed the ostial location change along the cardiac cycle. In addition, the high ostial location in the systolic phase was an independent predictor of MACE along with age but

this was not true in the diastolic phase.

We observed that all changes in ostial locations were from a high ostial location in the diastolic phase to a low ostial location in the systolic phase. There was no case of low ostial location changing to high ostial location from the diastolic to systolic phase, respectively, in the present study. Considering the changes that occur in the dimension of ventricles and great vessels during the cardiac cycle, the low ostial location in the diastolic phase and high ostial location in the systolic phase seems to be related to the most dangerous subtype of AORL with an interarterial course. Therefore, large-scale observations are warranted in the future, especially for patients in whom a low ostial location in the diastolic phase changes to a high ostial location in the systolic phase, so that we can understand the clinical significance of a high ostial location of AORL with an interarterial course in the diastolic phase.

As expected, a high ostial location in the systolic phase was a significant predictor of MACE even after adjusting for age. However, other CT characteristics did not significantly predict MACE in the present study. There may be issues regarding measurement accuracy due to the very small size of the ostium. In addition, the administration of nitroglycerin in some patients will affect anatomic features, particularly those related to the vessel diameter.

Furthermore, we supposed that each patient would have different thresholds of the ostial figures for MACE, and absolute cut-off values might not be important. However, further studies are needed to understand the accurate pathophysiology related to ostial figures in this anomaly.

Because not all patients underwent functional studies in the present study, the results of functional studies were not included in the Cox regression analysis. Similar findings were also observed in prior studies [5,15,16]. These previous studies concluded that ischemic conditions in the stress test cannot stratify risk for an anomalous origin of the coronary artery arising from the opposite sinus with an interarterial course, although the exact mechanism behind this condition has yet to be elucidated. Therefore, the possibility of MACE cannot be excluded by negative results in stress tests, and clinical risk should be considered along with the anatomical features of the ostium.

Young age is a well-known risk factor for AORL with an interarterial course [17]. Likewise, we observed that age was an independent predictor of MACE in the present study. In a retrospective study of cardiac CT, the anomaly might be discovered and included by chance, especially in older patients who are generally more likely to undergo cardiac CT for other reasons than younger patients. For this reason, younger age might seem to have a greater impact on MACE occurrence in the present study. Based on our study results, we would like to suggest the following workup scheme. We first recommend a dynamic evaluation with cardiac CT if an AORL with an interarterial course is found in younger symptomatic patients. If a high-type ostium during the systolic phase is determined, we carefully recommend surgical treatment. Otherwise, close observation instead of surgical treatment is recommended.

There are several limitations in this study. First, this study had a retrospective design, and only patients with cardiac CT images from both diastolic and systolic phases with retrospective ECG gating were included. Therefore, a selection bias could exist. Second, six of the 13 MACE were surgical treatment. However, two of the six patients had unstable angina before surgery and the other four patients had recurrent typical angina that had to be considered for surgical treatment. Third, the ECG pulsing window with 30%–80% of the R-R interval might not be sufficient to enable exact evaluation of the whole cardiac cycle. In addition, we used cardiac CT images with an already fixed cardiac cycle. Because the raw data were unavailable, further image reconstruction could not be done to improve

image quality. Hence, different degrees of inter-observer agreements might be obtained for CT characteristics between the cardiac phases.

In conclusion, the ostial location of AORL with an interarterial course changes during the cardiac cycle as seen on CT, and high ostial location in the systolic phase was an independent predictor of MACE. Further studies with retrospective cardiac CT data from larger populations are needed to fully understand this anomaly and to fully develop a practical risk stratification system for clinical use.

Supplement

The Supplement is available with this article at <https://doi.org/10.3348/kjr.2021.0270>.

Supplementary Movie Legends

Movie 1. Cardiac cine images with a representative case of changes in ostial location during the cardiac cycle.

Cine images with maximal intensity projection on the sagittal plane show ostial location change from high in the diastolic phase to low in the systolic phase. The second replay of the cine image is marked with asterisks (red asterisk, ostium of the anomalous right coronary artery; yellow asterisk, pulmonary valve annulus).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Kyunghwa Han who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Hye-Jeong Lee. Data curation: Hye-Jeong Lee, Jin-Young Kim, Yoo Jin Hong. Formal analysis: Hye-Jeong Lee, Kyunghwa Han. Investigation: Hye-Jeong Lee, Jin-Young Kim, Yoo Jin Hong. Methodology: Hye-Jeong Lee, Kyunghwa Han. Writing—original draft: Hye-Jeong Lee, Jin-Young Kim. Writing—review & editing: Yoo Jin Hong, Suji Lee, Young Jin Kim, Byoung Wook Choi.

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