

Clinical Features and Prognosis of Japanese Patients With Anomalous Origin of the Coronary Artery

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Anomalous origin of the coronary artery can lead to angina pectoris, acute myocardial infarction or even sudden death in the absence of atherosclerosis. However, in Japan, this anomaly is usually treated medically rather than surgically. To clarify the clinical features of anomalous origin of the coronary artery in Japanese and the prognosis of such patients who are treated medically, we reviewed 56 patients with anomalous origin of the coronary arteries. The mean age of these patients was 55.9 ± 11.5 years. Anomalous origin of the right coronary artery from the left sinus of Valsalva was seen most frequently (78.6%). In contrast, we found no cases of anomalous origin of the left coronary artery from the right sinus of Valsalva traversing between the aorta and the pulmonary trunk. A history of syncope (14.3%) and aortic regurgitation (21.4%) was frequent and serious complications during exercise stress testing occurred in 5 patients. These patients were treated medically, such as by limiting exercise or by the oral administration of medicine. During the follow up period (mean 5.6 ± 4.2 years), death directly related to anomalous origin of the coronary artery was not found despite the lack of surgical treatment. Our results suggest that the prognosis of these middle-aged-to-elderly patients without atherosclerosis is relatively good, despite the lack of surgical treatment.

(*Jpn Circ J* 1996; **60**: 731–741)

ANOMALIES of the coronary artery are defined as anatomical variants found in less than 1% of normal individuals¹. Among these anomalies, anomalous origin of the coronary artery can lead to angina pectoris, acute myocardial infarction or sudden death, even in the absence of atherosclerosis^{2–25}. Although this anomaly

is sometimes treated surgically^{9,15–17} surgical treatment is rare in Japan^{26–29}. The objective of this study was to clarify the clinical features of anomalous origin of the coronary artery in Japanese and the prognosis of these patients without surgical treatment.

METHODS

Patients

Of 17,731 patients who underwent diagnostic coronary arteriography between

Key words:

Key words:
Anomalous origin of the coronary artery
Medical treatment
Prognosis
Aortic regurgitation

(Received November 14, 1995; accepted March 14, 1996)

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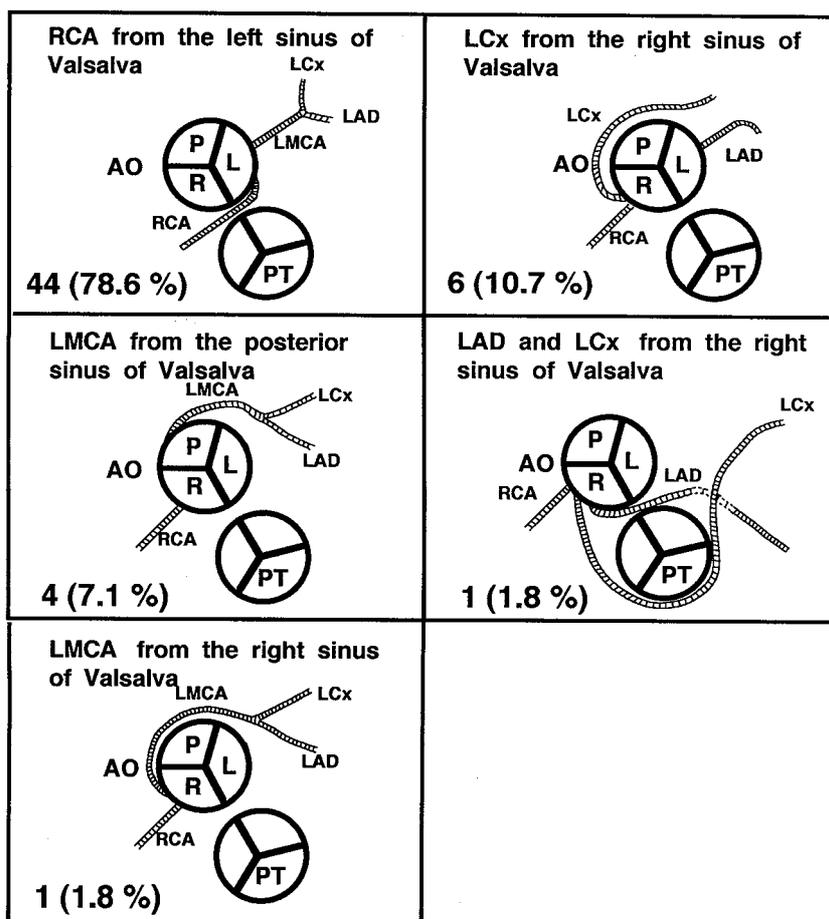


Fig 1. Diagrammatic representation of aberrant coronary artery patterns.
 RCA=right coronary artery, LCx=left circumflex coronary artery, LMCA=left main coronary artery, LAD=left anterior descending coronary artery, AO=aorta, PT=pulmonary trunk, R=right sinus of Valsalva, L=left sinus of Valsalva, P=posterior sinus of Valsalva.

January 1968 to June 1994, 56 patients (0.32%) had anomalous origin of the coronary arteries. We retrospectively reviewed the clinical records of these 56 patients (41 men, 15 women, aged 32 to 85 years) and obtained follow-up data by questionnaires and telephone interviews. Patients with a single coronary artery, a congenital hypoplastic coronary artery, and anomalous origin of the coronary artery from the pulmonary trunk were excluded.

Cardiac Catheterization

Coronary arteriography was performed either by the Judkins femoral method or the Sones brachial method. Ergonovine was injected into the coronary artery in patients suspected to have spasm of the coronary artery for a provocation test. Coronary arteriograms were reviewed by at least three

arteriographers.

Exercise Stress Testing

Exercise stress tests included Master's double or triple tow step test, a treadmill exercise test or exercise thallium-201 myocardial single photon emission computed tomography (exercise ^{201}Tl SPECT) using an upright or supine bicycle ergometer. A positive Master's test was defined according to the criteria of Master and Rosenfeld.³⁰ A positive treadmill exercise test was defined as the appearance of ≥ 1 mm (0.1 mV) horizontal or downsloping ST-segment depression at 80 msec after the J point.

Prognosis and the Incidence of Cardiac Events in Patients Without Organic Coronary Stenosis

We evaluated the prognosis of patients

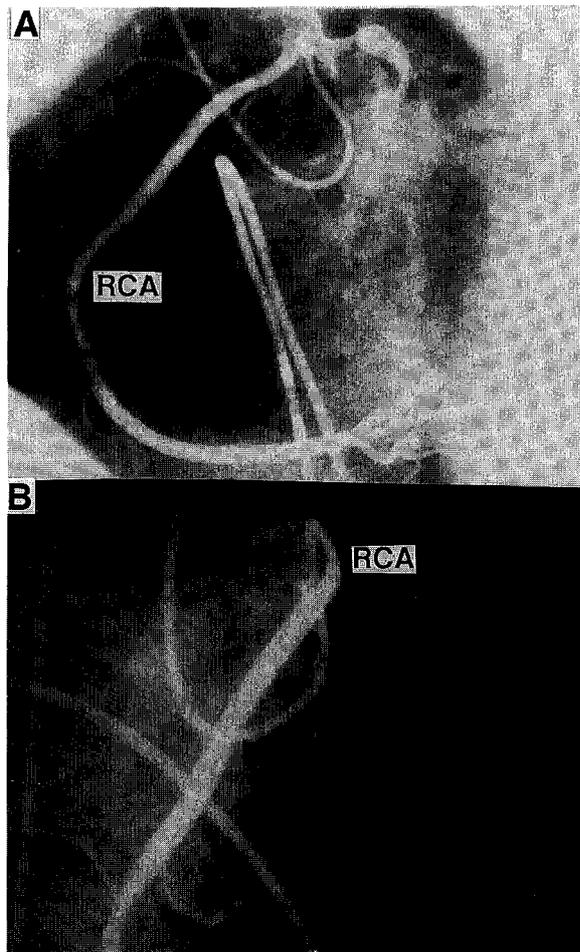


Fig 2. (A) Left anterior oblique view and (B) right anterior oblique view of anomalous origin of the right coronary artery from the left sinus of Valsalva.

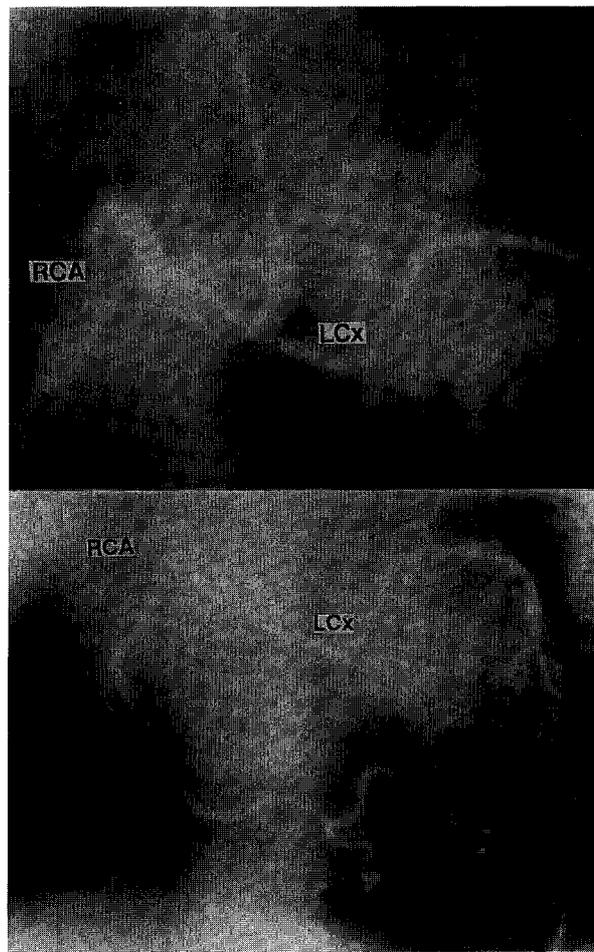


Fig 3. Left anterior oblique view of the left circumflex coronary artery originating from the right sinus of Valsalva.

without significant atherosclerotic coronary artery stenosis to investigate the influence of anomalous origin of the coronary artery on the prognosis. Follow-up data was available for 44 (97.8%) of 45 patients without organic coronary stenosis.

Statistical Analysis

Values are expressed as the mean \pm SD. Survival curves and event-free curves were calculated according to the Kaplan-Meier actuarial method. We compared difference in the prevalence of sexes and the incidence of aortic regurgitation between the 17,675 patients without anomalous origin of the coronary artery who underwent diagnostic coronary arteriography (control subjects) and patients with anomalous origin of the coronary artery by a chi-square analysis. A p value <0.05 was accepted as statistically

significant.

RESULTS

Type of Anomaly (Fig 1)

The right coronary artery originated from the left sinus of Valsalva in 44 (78.6%) of the 56 patients (Fig 2). The anomalous right coronary artery traversed between the aorta and the pulmonary trunk in all of these 44 patients. In 6 patients (10.7%), the left circumflex coronary artery originated from the right sinus of Valsalva and traversed posterior to the aorta (Fig 3). In 4 patients (7.1%), the left coronary artery originated from the posterior sinus of Valsalva and traversed posterior to the aorta (Fig 4). The left coronary artery originated from the right sinus of Valsalva in 1 patient (1.8%) and traversed posterior to the aorta (Fig 5). The

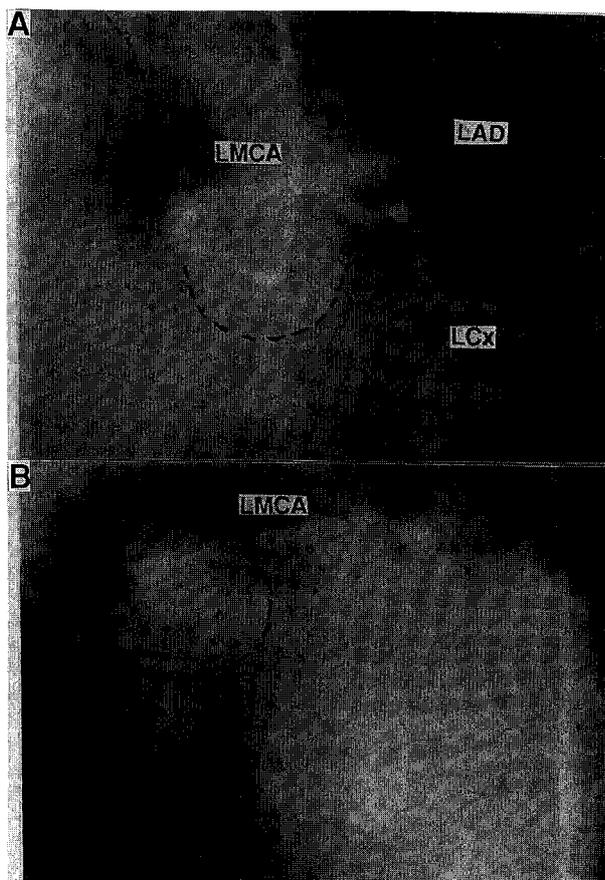


Fig 4. (A) Right anterior oblique view and (B) left anterior oblique view of anomalous origin of the left coronary artery from the posterior sinus of Valsalva.

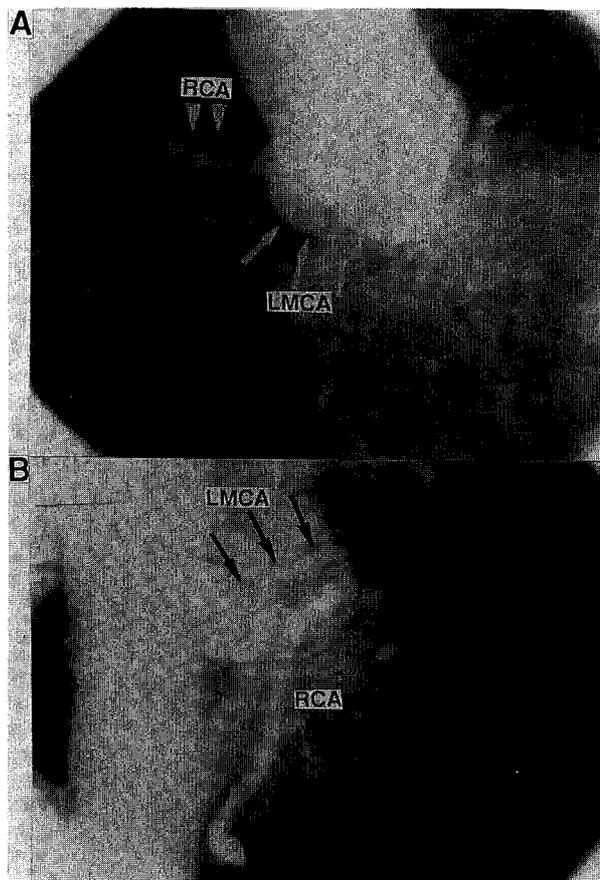


Fig 5. (A) Left anterior oblique view and (B) right anterior oblique view of anomalous origin of the left coronary artery from the right sinus of Valsalva.

left anterior descending coronary artery and the left circumflex coronary artery originated separately from the right sinus of Valsalva in 1 patient (1.8%). In this patient, the anomalous left anterior descending coronary artery traversed between the aorta and the pulmonary trunk and the left circumflex coronary artery traversed anterior to the pulmonary trunk (Fig 6).

Stenosis of the Anomalous Coronary Artery

Significant coronary atherosclerosis ($\geq 75\%$ stenosis) was present in 11 (19.6%) of the 56 patients, but significant coronary atherosclerosis of the anomalous coronary artery was present in only 1 of these 11 patients.

Clinical Features (Table I)

There were 41 men and 15 women. We found no sex difference between patients with anomalous origin of the coronary artery

and control subjects (men 12,129, women 5,546) ($P=0.46$). The mean age was 55.9 ± 11.5 years. A history of syncope was present in 8 (14.3%) of the 56 patients. Seven of these 8 patients did not have significant coronary atherosclerosis and 1 had 99% stenosis of the left circumflex coronary artery. In 4 patients, syncope occurred during physical exercise, such as while playing baseball, badminton or mountain climbing, and during thallium-201 exercise scintigraphy using a bicycle ergometer. In the remaining 4 patients, syncope occurred during daily activities, such as while taking a bath or drinking liquids. Ventricular tachycardia was detected in 1 of the 5 patients with anomalous origin of the right coronary artery. The incidence of aortic regurgitation in control subjects (2.2%) was significantly lower than that in patients with anomalous origin of the coronary artery (12 of 56, 21.4%; $p < 0.001$). Evidence of myocardial

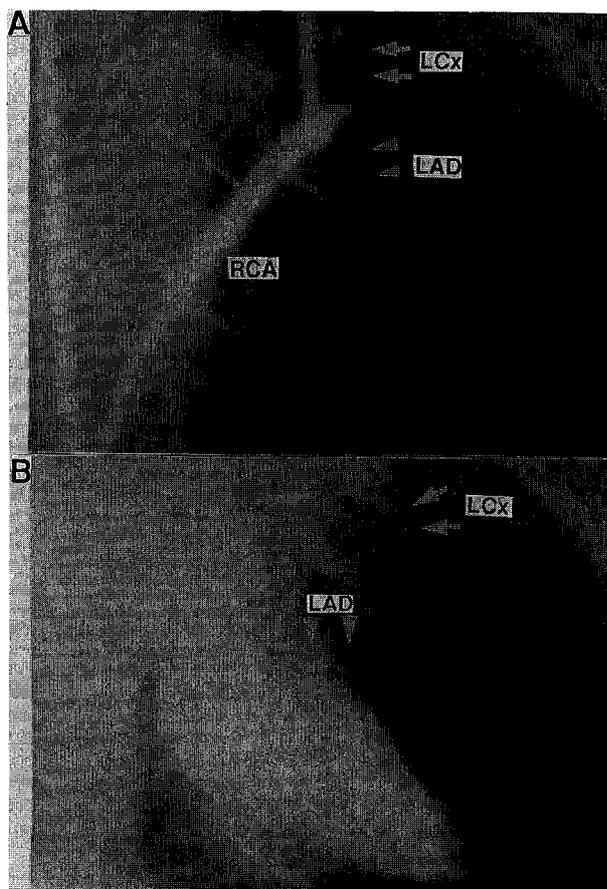


Fig 6. (A) Left anterior descending coronary artery and left circumflex coronary artery originating separately from the right sinus of Valsalva. (B) The left anterior descending coronary artery traversed between the aorta and the pulmonary trunk and the left circumflex coronary artery traversed anterior to the pulmonary trunk.

infarction was present in 1 (2.2%) of the 45 patients without atherosclerosis and in 7 (63.6%) of the 11 patients with atherosclerosis. Myocardial infarctions in patients with atherosclerosis were related to significant atherosclerosis of the coronary arteries. Conduction disturbances were present in 4 patients and other cardiac anomalies were seen in 3 patients.

Symptoms and Indications for Cardiac Catheterization in 45 Patients Without Organic Coronary Stenosis

Chest pain precipitated by exertion was present in 18 patients (40%), chest pain at rest in 9 patients (20%), chest pain at rest and precipitated by exertion in 8 patients (18%), palpitations in 2 patients (4%), dysp-

TABLE I CLINICAL FEATURES OF 56 PATIENTS

Gender	
Male	41 (73.2%)
Female	15 (26.8%)
Age at diagnosis	
	55.9 ± 11.5
History of syncope	
RCA from the left sinus of Valsalva	5 (*2)
LMCA from the posterior sinus of Valsalva	2 (*2)
LCx from the right sinus of Valsalva	1
Aortic regurgitation	
Grade I	5
Grade II	4
Grade III	2
Grade IV	1
Conduction disturbance	
Complete AV block	1 (1.8%)
CRBBB	3 (5.4%)
Other cardiac anomalies	
Wolff-Parkinson-White syndrome	1 (1.8%)
Bicuspid aortic valve	1 (1.8%)
Ventricular septal defect	1 (1.8%)

*syncope during physical exercise

AV=atrioventricular CRBBB=complete right bundle branch block

nea on exertion in 1 patient (2%), syncope in 1 patient (2%), and no symptoms in 6 patients (13%). The indication for coronary angiography was chest pain consistent with angina pectoris in 35 patients. Coronary arteriography was performed in 3 asymptomatic patients for preoperative study of aortic regurgitation, and anomalous origin of the coronary artery was found by chance. Coronary arteriography was performed in the other 3 asymptomatic patients because of electrocardiographic abnormalities.

Exercise Stress Testing in Patients Without Organic Coronary Stenosis (Table II)

Of the 33 patients without organic coronary stenosis who underwent exercise stress testing, 16 (48.5%) had positive results. Exercise ^{201}Tl SPECT was performed in 9 patients. Myocardial ischemia was detected in the area of the anomalous origin of the coronary artery in 4 patients (44.4%). Serious complications during treadmill exercise tests or exercise ^{201}Tl SPECT were found in 5 patients: 2 patients showed ventricular

TABLE II POSITIVE EXERCISE STRESS TESTS IN PATIENTS WITHOUT ORGANIC CORONARY STENOSIS

(n=33)

Type	Treadmill test or Master's 2-step test	Exercise ²⁰¹ TL SPECT	Complications
RCA from the left sinus of Valsalva	10/22	3/4	Exercise-induced hypotension 2 Ventricular tachycardia 2
LCx from the right sinus of Valsalva	3/5	1/2	
LMCA from the posterior sinus of Valsalva	1/4	0/2	Exercise-induced hypotension 1
LMCA from the right sinus of Valsalva	1/1		
LAD and LCx from the right sinus of Valsalva	1/1	0/1	
Total	16/33 (48.5%)	4/9 (44.4%)	5/33 (15.2%)

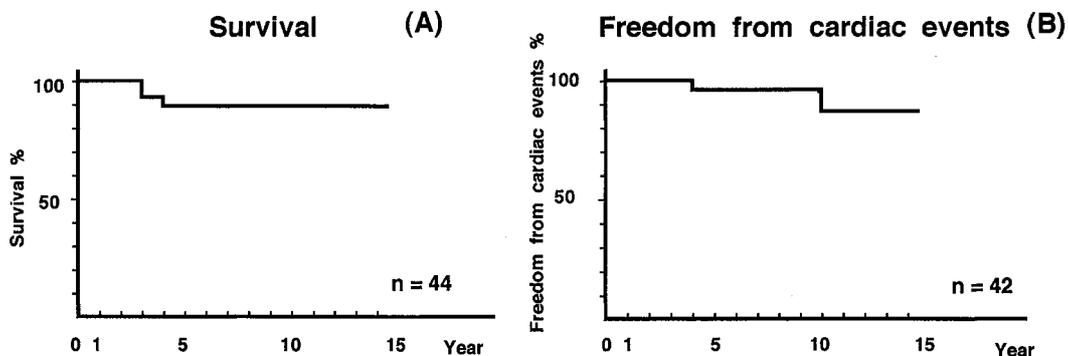


Fig 7. A: Survival curve and B: event-free curve. Curves were calculated according to the Kaplan-Meier actuarial method.

tachycardia and 3 patients showed exercise-induced hypotension.

Ergonovine Provocation Tests

Provocation tests were positive in 2 of 7 patients who were suspected of having spasm of the coronary artery.

Treatment of Patients Without Organic Coronary Stenosis

None of the patients underwent surgery to treat their anomalies. Four of the 44 patients available for follow-up were treated simply by limiting exercise. Limitation of exercise and drug therapy were prescribed in 12 patients, drug therapy alone in 13 patients, and no treatment in 15 patients. Medication consisted of nitrates, calcium-channel blockers, beta-adrenergic antagonists or antiarrhythmic drugs. Sublingual nitroglycerin was effective in 11 (68.8%) of 16 patients. Of the 29 patients who received

some kind of treatment, 26 complained of symptoms before treatment, and these symptoms improved in 18 patients (69.2%) after treatment.

Follow-Up Data

The follow-up period ranged from 2 months to 14.5 years (mean 5.6 ± 4.2 years) in 44 of 45 patients without significant coronary artery stenosis. There were 3 deaths during the follow-up period: 1 patient died of cancer, one of cerebral infarction, and one of severe aortic stenosis. Both the 5-year and 10-year survival rates were 89.2% (Fig 7A). There were no deaths directly attributable to anomalous origin of the coronary artery. Cardiac events (cardiac death, acute myocardial infarction or syncope) occurred in 2 patients during the follow-up period; syncope in 1 patient who did not receive treatment, and severe aortic stenosis in 1 patient who died. The 5-year and

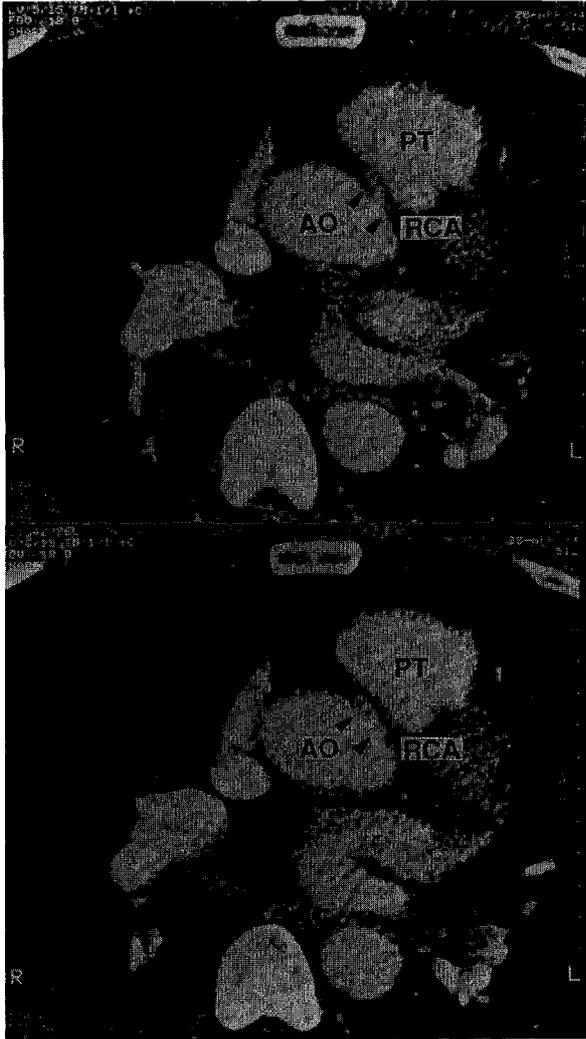


Fig 8. Ultrafast computed tomography (UFT) of anomalous origin of the right coronary artery from the left sinus of Valsalva. UFT demonstrated an acute angle of takeoff from the aorta of the anomalous right coronary artery, and the proximal portion of the right coronary artery traversed between the aorta and pulmonary trunk.

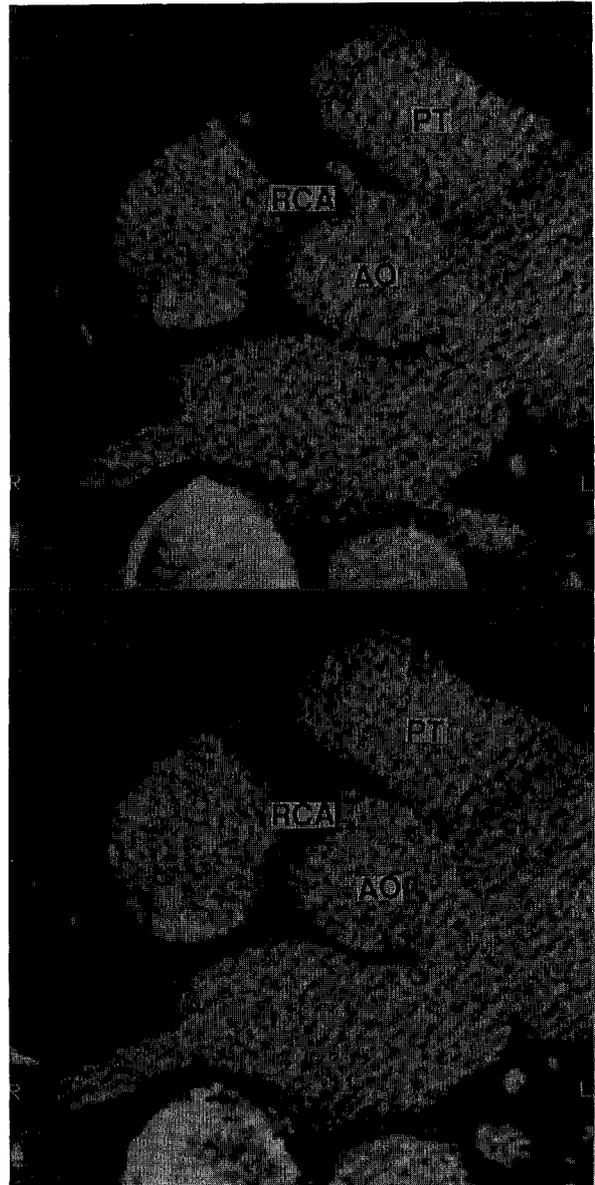


Fig 9. Ultrafast computed tomography of the right coronary of a normal subject. The right coronary artery originates vertically from the aorta.

10-year event-free rates were 95.8% and 87.1%, respectively (Fig 7B).

DISCUSSION

Increased use of cardiac catheterization has led to the increased detection of anomalous origin of the coronary artery. The incidence, type and clinical features of anomalous origin of the coronary artery in patients in the United States have been described elsewhere^{2,5,21,22,31,32} In the US, the incidence of anomalous origin of the

coronary artery has been reported to range from 0.3% to 0.64%^{2,31,32} In the present study, anomalous origin of the coronary artery was present in 0.32% of patients who underwent diagnostic coronary arteriography. This incidence appears to be consistent with those in previous reports^{2,31,32} Thus, the incidence of anomalous origin of the coronary artery is similar in Japan and the US. Although Kimbiris et al² reported that this anomaly was more common in men than in women, we found no sex difference in the present study. One possible explanation for

why most of the subjects in our study were men is that more men underwent coronary arteriography.

This anomaly can lead to angina pectoris, acute myocardial infarction or sudden death, even in the absence of atherosclerosis.²⁻²⁵ In the US, surgical procedures such as aortocoronary bypass or anatomical correction of the ostium of the anomalous coronary artery are sometimes performed to prevent sudden death in these patients.^{9,15} In Japan, surgery is not performed unless the anomaly is associated with coronary atherosclerosis.²⁶⁻²⁹ In the present study, none of the patients without significant atherosclerosis underwent surgery.

Type of Anomaly

The most common type of anomaly in the US is origination of the left circumflex coronary artery from the right sinus of Valsalva.^{2,31,32} Kimbiris et al reported that anomalous origin of the left circumflex artery accounted for 57.8% of all types of anomalies.² In the present study, this type of anomaly accounted for only 10.7% of the anomalies, while the right coronary artery originated from the left sinus of Valsalva in 78.6% of the patients. None of our middle-aged-to-elderly patients exhibited a left coronary artery that originated from the right sinus of Valsalva and traversed between the aorta and the pulmonary trunk. This type of anomaly has been considered the most risky anomaly associated with exercise-related sudden death in younger subjects.^{2,5-7}

Clinical Significance of Anomalous Origin of the Coronary Artery

Although anomalous origin of the coronary artery was once considered to be benign,^{33,34} there are now numerous reports that this anomaly can lead to angina pectoris, acute myocardial infarction or sudden death.²⁻²⁵ The risk of these serious complications has been particularly noted for anomalous origin of the left coronary artery from the right coronary sinus traversing between the aorta and the pulmonary trunk.^{2,5-7} Acute myocardial infarction and sudden death have also been reported in patients with anomalous origin of the left circumflex coronary artery,^{11,12} and complica-

tions have been observed in patients with anomalous origin of the right coronary artery, some of whom have undergone surgery.¹⁴⁻¹⁷ In the present study, 5 patients with anomalous origin of the right coronary artery had histories of syncope, 2 patients exhibited exercise-induced hypotension associated with myocardial ischemia, and 2 patient exhibited exercise-induced ventricular tachycardia. These findings suggest that anomalous origin of the right coronary artery from the left sinus of Valsalva may be associated with a risk of significant cardiovascular events, even in the absence of atherosclerosis.

Symptoms of Patients Without Organic Coronary Stenosis

Chest pain precipitated by exertion has been observed in patients with anomalous origin of the coronary artery without atherosclerosis,^{3,9,11,13,15} perhaps as the result of exercise-induced myocardial ischemia. There are several hypotheses regarding the pathogenesis of exercise-induced myocardial ischemia in patients with coronary artery anomalies. One is that the oblique takeoff of the anomalous artery produces a slit-like orifice in the aortic wall that can collapse like a valve during exercise.^{5,9,16,18-20} Another hypothesis is that when the anomalous artery is located between the aorta and the pulmonary trunk, it is compressed by these two great vessels, particularly during exercise.^{4,6,14,18,19} However, detailed information regarding the proximal portion of the anomalous coronary artery, such as the angle of takeoff and its proximal course, can not be acquired by coronary angiography alone. Based on autopsy findings, Virmani et al²⁰ emphasized that anomalous origin of the coronary artery is not uniformly fatal and that the clinical significance of this anomaly depends on its proximal structure. In the present study, most of the patients only underwent coronary angiography. Therefore, the anatomical differences between the proximal portions of each anomalous coronary artery are still unclear. Transesophageal echocardiography,³⁵ ultrafast computed tomography (Figs 8, 9),^{36,37} and fast gradient-echo magnetic resonance coronary angiography^{38,39} have recently proven to be useful for evaluating the prox-

imal portion of the anomalous coronary artery. These new techniques will be used in further studies to analyze the mechanism of exercise-induced myocardial ischemia associated with anomalous origin of the coronary artery. In the present study, 48.5% of the patients who complained of chest pain had chest pain at rest. Such chest pain at rest is not adequately explained by either of the two hypotheses cited above. Provocation tests were positive in 2 of 7 patients in whom selective coronary angiography was performed in the present study. Maddoux et al²³ detected vasospasm of the left coronary artery originating from the right sinus of Valsalva in a patient with unstable angina at rest. Roynard et al²⁴ found no atherosclerosis and a negative provocation test in a patient with anomalous origin of the left anterior descending coronary artery who had unstable angina at rest. Therefore, the mechanism of this patient's angina was unclear. In the present study, nitrates or calcium-channel blocker were effective in the 17 patients with chest pain at rest. Although the mechanism of the chest pain at rest was unclear, we believe that vasospasm of the coronary artery may have been related to resting angina in some patients.

Anomalous Origin of the Coronary Artery and Associated Cardiac Disease

In the present study, aortic regurgitation was significantly more common in patients than in control subjects. The incidence of aortic regurgitation in control subjects who had undergone diagnostic coronary arteriography in our hospitals was 2.2%. In contrast, Kimbiris et al² detected aortic valvular disease in 9 of 45 patients (20%). In 3 patients in the present study, anomalous origin of the coronary artery was diagnosed during preoperative catheterization for aortic regurgitation, suggesting that there may be a close association between these conditions. Among our 33 patients without organic coronary stenosis who underwent exercise stress tests, 4 of the 16 patients who had positive exercise stress tests and 3 of the 17 patients who had negative tests exhibited aortic regurgitation. Therefore, no relationship was found between aortic regurgitation and the results of exercise stress tests in the present study. A higher incidence of associ-

ated syncope was also reported by Kimbiris et al². Although the mechanism of syncope associated with anomalous origin of the coronary artery is not well understood, syncope often occurs during physical exercise^{7,17}. In the present study, syncope occurred during physical exercise in 4 patients, and 3 of these 4 showed positive treadmill exercise tests. Maddoux et al²³ reported a case of anomalous origin of the left coronary artery in which ventricular tachycardia and vasospasm were thought to have produced syncope, and Bengte et al¹⁴ reported a case of anomalous origin of the right coronary artery in which third-degree atrioventricular block was thought to have produced syncope.

Stenosis of Anomalous Coronary Artery

Only 1 of the 11 patients with significant coronary atherosclerosis in the present study had significant atherosclerosis of the anomalous coronary artery. Click et al²⁵ found no significant difference in the degree of stenosis between anomalous coronary arteries and arteries in matched control subjects without anomalies.

Survival and Cardiac Events

Medical treatment consisting of limitation of exercise or oral medications was recommended in 29 of the 44 patients without significant coronary artery stenosis. There were no deaths directly related to anomalous origin of the coronary artery, and no acute myocardial infarctions occurred during the follow-up period. Syncope occurred in 1 patient who did not receive any treatment during the follow-up period. Our results suggest that the prognosis of these middle-aged-to-elderly patients without atherosclerosis is relatively good, despite the lack of surgical treatment. However, because of possible serious complications during exercise, surgical intervention should be considered in patients who want to engage in vigorous sports or physically demanding labor.

Limitations

The mean age at diagnosis of our patients was 55.9 ± 11.5 years (range 32 to 85 years). Previous reports have suggested that sudden death is more likely to occur in younger patients^{6,19} possibly because teenagers and

individuals in their 20s may exercise more vigorously. None of our patients had anomalous origin of the left coronary artery from the right sinus of Valsalva traversing between the aorta and the pulmonary trunk. Therefore, our conclusions are not applicable to patients with this type of anomaly.

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