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Coronary CT Angiography in Takayasu Arteritis

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OBJECTIVES The aim of this study was to use coronary computed tomographic (CT) angiography to characterize coronary artery involvement in patients with known Takayasu arteritis who present with anginal chest pain or shortness of breath.

BACKGROUND Takayasu arteritis is a primary vasculitis of the large vessels, which mainly affects the aorta and its branches but can also involve the coronary arteries. Coronary CT angiography allows visualization of the coronary vessels and can be used to detect both stenotic and nonstenotic coronary artery lesions.

METHODS Eighteen consecutive patients with Takayasu arteritis and angina (typical or atypical) and/or dyspnea underwent contrast-enhanced 64-slice coronary CT angiography. The arterial injury was classified according to the Numano classification. Three patients had prior known coronary artery disease. Coronary arteries were evaluated concerning the presence of obstructive and nonobstructive lesions, and differences between the clinical presentations of patients with and without coronary artery involvement on CT angiography were analyzed.

RESULTS Coronary artery involvement was found in 8 patients (44.4%), 3 of them with clinical activity. A total of 19 coronary lesions were present (13 in ostial locations, 5 in proximal coronary artery segments, and 1 in a mid segment). Eight lesions exceeded 50% diameter reduction (2 in ostial locations and 6 in proximal coronary artery segments). Median disease duration was significantly different between patients with coronary artery involvement (176 months; range 13 to 282 months) compared with those without (21 months; range 1 to 142 months) ($p = 0.013$).

CONCLUSIONS Coronary CT angiography allows the assessment of coronary artery involvement in patients with Takayasu arteritis. These data confirm prior observations that most coronary lesions are in ostial or proximal coronary artery locations. Disease duration in patients with coronary artery involvement is longer than in patients without. (J Am Coll Cardiol Img 2011;4:958–66) © 2011 by the American College of Cardiology Foundation

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Takayasu arteritis (TA) is a primary large vessel vasculitis of unknown origin that mainly affects the aorta and its branches. It occurs worldwide and is more common in young women (median age at onset is 25 years). The incidence of TA in the United States is approximately 2.6 per 1 million persons, but it can be substantially different in other parts of the world (1–3). Both aneurysms and, more frequently, stenoses of the large vessels can occur. Up to 80% of patients present with hypertension, claudication is frequent, and in as many as 53% of patients, myocardial perfusion abnormalities were observed on Thallium-^{201} stress scintigraphy (4). In patient series with TA, between 7% and 29% of patients were found to have coronary involvement. In the vast majority of cases, the coronary ostial and proximal segments were affected (4–7). One series reported that 87.5% of hemodynamically relevant coronary artery stenoses were in ostial locations (7).

Invasive coronary angiography is the clinical gold standard for the diagnosis of coronary artery stenoses. However, it is not free of complications, arterial access can be difficult in patients with TA, and it may fail to visualize early atherosclerotic changes of the coronary arteries (8). Because of rapid technical developments in recent years, multidetector computed tomography (MDCT) has developed into a clinically useful method for coronary artery visualization in selected patients (9–11). Accuracy for stenoses detection is high if image quality is good (12–15), and because of its high negative predictive value, coronary computed tomographic (CT) angiography is most frequently used to exclude significant coronary stenoses (10,11). Coronary angiography using MDCT can be used to identify, and to a certain extent characterize, coronary atherosclerotic plaque (16–21). Furthermore, MDCT is a reliable tool for the diagnosis and severity assessment of aorto-ostial lesions (22,23).

The objective of this work was to systematically analyze coronary CT angiographic findings in a group of patients with TA who presented with angina symptoms or dyspnea to identify and describe patterns of coronary artery involvement.

METHODS

Study population. Among a cohort of 80 patients with TA, we included 18 consecutive patients who presented with dyspnea or angina (typical or atypical) between March 2006 and April 2009. The patients were sent to MDCT coronary angiography to rule out coronary involvement as a cause of symptoms, because coronary involvement in TA is mainly ostial and MDCT has been demonstrated to be useful in the diagnosis of this kind of lesion (22,23).

Inclusion criteria were established diagnosis of TA according to the American College of Rheumatology (at least 3 of the following criteria: age ≤40 years at disease onset, claudication of extremities, decreased brachial artery pressure, blood pressure difference >10 mm Hg between the arms, bruit over the subclavian arteries or aorta, and abnormal arteriographic results) (24) and angina and/or dyspnea. We classified patients according to the Numano classification into 6 types (Fig. 1) (25).

Typical angina was considered present if patients reported: 1) pre-cordial chest pain or discomfort that was; 2) caused by exertion or emotional stress; and was 3) relieved by rest and/or nitroglycerin. Atypical angina was defined if the patient had chest pain or discomfort, lacking 1 of the characteristics of typical angina (26). Exclusion criteria were creatinine >1.5 mg/dl, hemodynamic instability, iodine allergy, and pregnancy. All patients received information about the purpose and objectives of the study and provided written informed consent.

ABBREVIATIONS AND ACRONYMS

CT = computed tomographic

MDCT = multidetector computed tomography

TA = Takayasu arteritis

Disease activity was evaluated according to the criteria of Dabague and Reyes (27), including clinical findings, blood counts, erythrocyte sedimentation rate, C-reactive protein level, and fibrinogen level (Table 1). Patients were considered to have active disease if they reached 5 or more points.

Coronary CT angiography. PATIENT PREPARATION. Patients with heart rates more than 65 beats/min received oral atenolol (50 to 100 mg) 1 h before coronary CT angiography, in the absence of contraindications. If a heart rate between 50 and 60 beats/min was not achieved, repeated doses of 5 mg intravenous metoprolol were given every 5 min up to a maximal dose of 15 mg or until the expected heart rate was obtained. Sublingual nitroglycerin (5 mg) was given immediately before image acquisition.

PROTOCOL. CT data were acquired using a 64-slice CT scanner (Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany). Scan parameters were set as follows: collimation 2 × 32 × 0.6 mm, gantry rotation time 330 ms, tube current 700 mA with electrocardiography-based tube current modulation, and tube voltage 100 to 120 kV. The scan length extended from the carina to the

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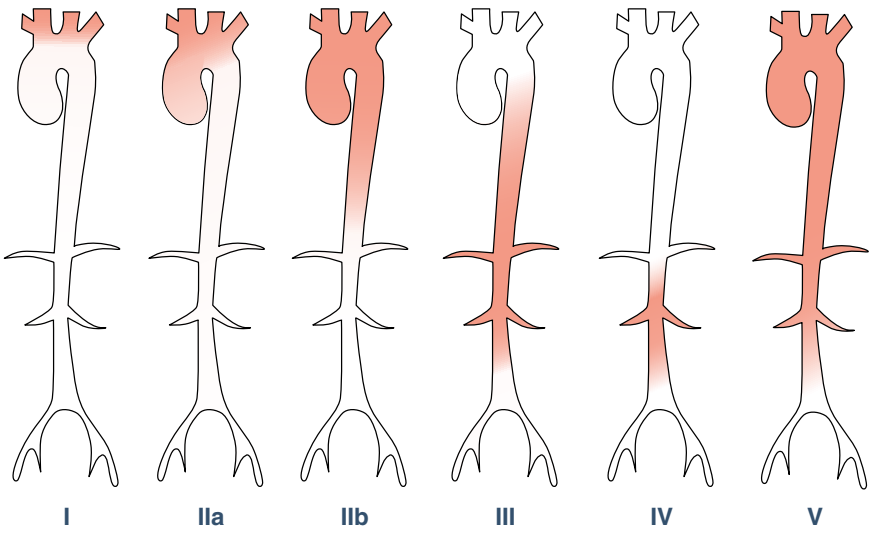

Figure 1. Numano Classification of Takayasu Arteritis

diaphragmatic crura. The entire heart was scanned during a single breath-hold. First a noncontrast scan was performed for calcium score. The coronary arteries were visualized without contrast medium, and 30 to 40 consecutive images were obtained at 3-mm intervals. Each calcified lesion exceeding the minimal criterion was scored using the algorithm developed by Min et al. (28), calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield units within this area. The total coronary artery calcium score was determined by summing individual lesion scores from each of 4 anatomic sites. Then, scan delay after contrast injection was determined using a test bolus technique with 20 ml of nonionic iodated contrast material (iopamidol 370 mg I/ml; Bayer Schering Pharma AG, Leverkusen, Germany). For coronary CT angiography, 90 ml of contrast material was administered at a rate of 5 ml/s. None of the patients showed adverse reactions to the contrast medium or complications during or after the study. The mean heart rate during coronary CT angiography was 62 ± 7 beats/min. The mean estimated effective radiation dose was 15 ± 2.4 mSv.

Images were analyzed on a dedicated workstation (Leonardo; Siemens Medical Systems). For the noncontrast images, the Agatston score for coronary calcification was determined by summing individual lesion scores from each of the left main, left anterior descending, left circumflex, and right coronary arteries.

For the contrast images, axial image datasets were reconstructed using retrospective electrocardiographic gating with 0.75-mm slice thickness at 0.5-mm intervals. All image reconstructions were performed at end-diastole (between 60% and 85% of the R-R interval). For analysis, image datasets were transferred to a post-processing workstation (Leonardo). All datasets were independently analyzed by 2 blinded experienced observers (A.M. and E.T.K.). Coronary arteries were analyzed according to a 15-segment model, and detectable coronary artery lesions were classified as: 1) nonsignificant (<50% luminal diameter reduction); 2) significant

Table 1. Clinical Criteria of Inflammatory Activity

3 Points	2 Points	1 Point
Angiodynia*	Subcutaneous nodules	Fever
Major ischemic event	Pulseless	Weight loss
	New bruit	Arthritis/arthralgia
		General malaise
The presence of 1 or both criteria results in 3 points. They are not summarized.	The presence of 1 or several criteria results in 2 points. They are not summarized.	The presence of 1 or several criteria results in 1 point. They are not summarized.

Normocytic normochromic anemia, leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate, elevated fibrinogen, elevated C-reactive protein (each results in 0.5 points, which are summarized). *Pain on palpation of the carotid artery.

(≥50% luminal diameter reduction); or 3) occlusion. In addition, coronary artery lesions were classified as noncalcified, partly calcified, or completely calcified. According to prior definition, ostial lesions were defined as any plaque within 3 mm of the takeoff of the coronary artery from the aorta (29).

Invasive coronary angiography. Five of 8 patients with coronary lesions on CT coronary angiography were referred to catheterization, 2 did not agree to undergo the procedure, and 1 did not have significant coronary lesions on MDCT, so invasive angiography was not considered necessary. In 3 patients, catheterization was diagnostic, and in 2 patients, catheterization was therapeutic.

Catheterization was performed in a standard fashion using a transfemoral approach in all patients. An experienced interventional cardiologist (E.G.) blinded to the CT results analyzed the severity of visually detected stenoses using offline quantitative coronary angiography. Angiographic images were magnified, and calibration was performed by measuring the known dimensions of the diagnostic catheter. Arterial contour detection used an automated edge detection algorithm and served to obtain the minimal luminal diameter and percent diameter stenoses in obstructive coronary lesions.

Statistical analysis. Continuous variables are expressed as mean ± SD or as medians and ranges (according to their distribution) and categorical variables as percents. Comparison between groups was done using Student t tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Statistical analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL).

RESULTS

The study cohort consisted of 16 women and 2 men, with a mean age of 37 ± 13 years. Seven patients presented with typical angina, 6 with atypical angina, and 5 with dyspnea. Nine patients had hypertension, 8 of whom had known renal artery involvement. No patient had a history of smoking or a family history of premature cardiovascular disease. One patient had diabetes, and 11 patients had known dyslipidemia. The median time interval between the initial diagnosis of TA and coronary CT angiography was 59 months (range 1 to 282 months) (Table 2).

Among the 18 patients studied, coronary CT angiography demonstrated coronary artery involvement in 8 patients (44.4%). Among them, 3 patients had histories of coronary artery disease. One 26-year-old woman had undergone prior percutaneous coronary intervention and stent placement into the left main coronary as well as coronary artery bypass surgery to the left anterior descending and circumflex coronary arteries at the age of 23 years. A 31-year-old woman had undergone bypass surgery to the right coronary artery at the age of 28 years, and a 49-year-old woman had experienced inferior myocardial infarction without reperfusion therapy at the age of 34 years.

Table 3 lists the coronary CT angiographic findings in patients with coronary artery involvement. Of the 8 patients with at least 1 detectable coronary artery lesion, 1 woman had only nonstenotic plaque, while 7 displayed at least 1 artery with more than 50% luminal narrowing. There were 8 significant or occlusive lesions, 7 of them in ostial locations (Figs. 2 and 3).

In addition, there were 11 coronary lesions with luminal narrowing of <50%, of which 6 were in ostial locations.

Four of 11 nonobstructive lesions were partly or completely calcified (Fig. 4A), while all 8 obstructive lesions were noncalcified. Of all 19 lesions, whether obstructive or nonobstructive, 13 were in ostial locations (Fig. 4B), 5 in proximal segments, and 1 in the mid segment of a coronary artery. It is of interest to note that the patient with detectable plaque but no stenoses, a 58-year-old woman with nonobstructive lesions in all coronary vessels, had more diffuse disease and a substantially higher calcium score (341 Agatston units) than all other patients. This potentially indicates a different mechanism of disease, such as conventional atherosclerosis.

Five of 8 patients with coronary artery involvement on CT angiography underwent invasive coronary angiography. In these 5 patients, CT angiography had demonstrated 6 significant stenoses, all of which were confirmed by invasive angiography. One significant lesion on invasive angiography was reported as nonsignificant on CT angiography, and 3 nonsignificant lesions observed on CT angiography were not identified on invasive angiography.

Comparison between patients with and without coronary involvement. Table 2 shows the clinical features of patients with and without detectable coronary artery involvement on coronary CT angiography. The mean age at presentation was 43 ± 10 years in patients with and 32 ± 12 years in patients without coronary involvement (p = NS). At the onset of symptoms, the mean age was 33 ± 10 years in patients with involvement and 27 ± 11 years in

Table 2. Population Demographics

	All Patients (n = 18)	Coronary Involvement (n = 8)	No Coronary Involvement (n = 10)	p Value
Women	16 (89%)	8 (100%)	8 (80%)	NS
Age (yrs)	36.8 ± 12.6	43.4 ± 10	31.6 ± 12	NS
Age at onset of symptoms (yrs)	29.3 ± 10.6	32.7 ± 10	26.7 ± 11	NS
Median of disease duration (months)	59 (1–282)	176 (13–282)	21 (1–142)	0.013
Numano type				
I	4	1	3	NS
IIa	1	1	0	NS
IV	1	0	1	NS
V	12	6	6	NS
Activity criteria	7	3	4	NS
Hypertension	9 (50.0%)	4 (50.0%)	5 (50.0%)	1
Diabetes	1 (5.5%)	0	1 (10.0%)	1
Dyslipidemia	11 (61.1%)	5 (62.5%)	6 (60.0%)	0.64
Prior coronary artery disease	3 (16.7%)	3 (37.5%)	0	0.043
Clinical presentation				
Typical angina	7(38.9%)	5 (62.5%)	2 (20.0%)	0.14
Atypical angina	6 (33.3%)	1 (12.5%)	5 (50.0%)	
Dyspnea	5 (27.8%)	2*(25.0%)	3 (30.0%)	
Diamond Forrester classification	21 (0.8–55.2)	25.8 (2.8–55.2)	13 (0.8–55.2)	0.2
Coronary calcium score	0 (0–341)	0.5 (0–341)	0 (0–0)	NS

Values are n (%), mean ± SD, or median (range). *One patient had dilated cardiomyopathy.

patients without involvement (p = NS). Nevertheless, there was a significant difference in disease duration between the two groups, with a median duration of 176 months (range 13 to 282 months) in patients with involvement compared with 21 months (range 1 to 142 months) in patients without

Table 3. Coronary CT Angiographic Findings in Patients With Detectable Coronary Artery Involvement

Patient	Age (yrs)	Sex	Symptoms	Calcium Score (Agatston score)	LM	LAD	Cx	RCA
1	45	F	Dyspnea	0	Ostium noncalcified occlusion	—	—	Ostium noncalcified stenosis <50%
2	48	F	Atypical angina	1.1	Ostium noncalcified stenosis <50%	—	—	Ostium noncalcified stenosis ≥50%
3	31	F	Typical angina	0	Ostium noncalcified stenoses ≥50%	—	—	Ostium noncalcified stenosis ≥50%
4	26	F	Typical angina	0	Ostium in-stent noncalcified stenoses ≥50%	—	—	Ostium noncalcified stenosis <50%
5	45	F	Typical angina	0	Ostium noncalcified occlusion	—	—	Ostium noncalcified stenosis <50%
6	49	F	Typical angina	9.6	—	Ostium noncalcified occlusion	—	Ostium noncalcified stenosis <50%
7	45	F	Typical angina	14	Proximal partly calcified stenosis <50%	Proximal noncalcified stenosis <50%	—	Mid noncalcified stenosis ≥50%
8	58	F	Dyspnea	341.3	Ostium calcified stenosis <50%	Proximal calcified stenosis <50%	Proximal calcified stenosis <50%	Proximal calcified stenosis <50%

CT = computed tomographic; Cx = circumflex coronary artery; F = female; LAD = left anterior descending coronary artery; LM = left main coronary artery; RCA = right coronary artery; — = no lesion.

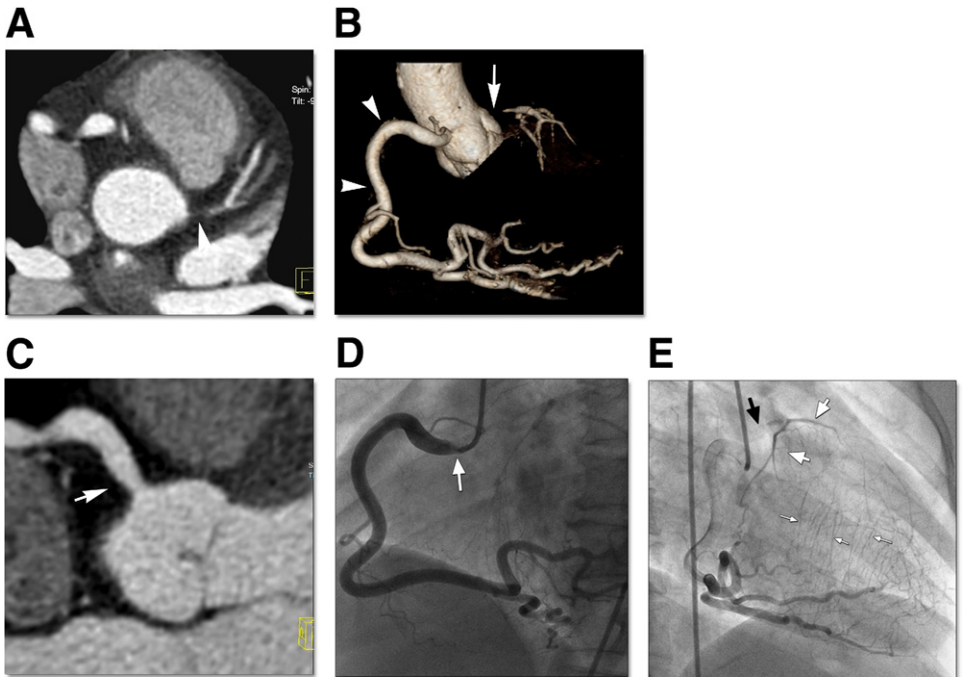

Figure 2. Occlusion of the Left Main Coronary Artery

Coronary computed tomographic (CT) and invasive angiography of a patient with Takayasu arteritis (TA) (Numano type IIb) with an ostial occlusion of the left main coronary artery and right coronary artery dilation as a compensatory mechanism. **(A)** Coronary CT angiographic axial image at the origin of the left main coronary trunk showing lack of opacification of the vessel (arrowhead) associated with negative remodeling. The vessel reconstitutes distally. **(B,C)** Conversely, the right coronary artery **(arrowheads)** is diffusely dilated as a compensatory mechanism, as easily demonstrated in this volume-rendering image, but its origin also shows mild tapering, as seen in the multiplanar reformat **(arrow in C)**. Again, notice the absence of contrast material within the lumen of the left main coronary trunk **(arrow in B)**. **(D,E)** Invasive coronary angiography confirms the right coronary ectasia and its tapering at the origin **(white arrow in D)** and the occlusion of the left main trunk **(black arrow in E)**. Multiple collaterals **(small white arrows in E)** to the left coronary circulation coming from the right coronary artery reconstituting mid-distal left anterior descending and left circumflex coronary arteries **(large white arrows in E)** are also seen. Most significant coronary lesions in patients with TA are ostial and noncalcified, as in this case.

coronary involvement ($p = 0.013$). Cardiovascular risk factors, including lipid levels, were not different between the 2 groups.

There was no difference in Numano type between patients with and without coronary artery affection. However, 6 of 8 patients with coronary artery lesions had ascending aortic involvement, compared with 3 of 10 patients without coronary involvement ($p = 0.07$).

Only 3 patients with coronary involvement had active disease according to the TA activity index (score > 5) at the time of coronary CT angiography. Four patients without detectable coronary involvement had activity criteria ($p = NS$).

Median coronary calcium scores were 0.5 and 0 Agatston units in patients with and without coronary artery involvement ($p = NS$). But all patients without coronary artery involvement had calcium scores of 0 Agatston units.

DISCUSSION

In a series of patients with TA who had chest pain and/or dyspnea and were studied using MDCT, we observed a high prevalence of coronary artery involvement. In this selected group, we found that 8 of 18 of the patients (44%) had coronary lesions, which is higher than the 7.6% found in pathology studies in nonselected patients with TA (6) and the 29.6% by selective invasive coronary angiography in patients with cardiovascular signs or symptoms (i.e., chest pain, ST segment changes, cardiomegaly, aortic regurgitation, systemic arteritis with severe stenoses, and renovascular hypertension) (7).

Coronary artery involvement in our patients was typically focal. Forty percent of all coronary artery lesions seen on CT were significant, with luminal diameter stenoses $\geq$ 50%. Almost all coronary lesions (95%) were ostial or proximal in location,

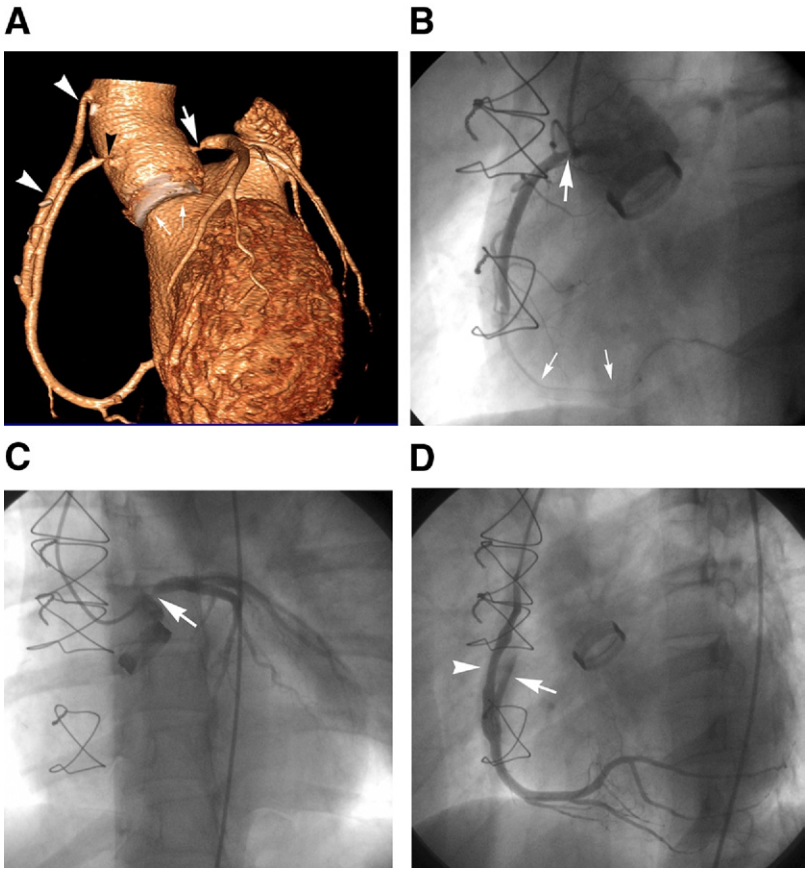

Figure 3. Significant Proximal Lesions

Coronary computed tomographic (CT) and conventional angiography of patient with Takayasu arteritis (TA) (Numano type V) and significant noncalcified lesions in the proximal right and left coronary arteries. Thirty-one-year-old woman with TA and a history of surgical revascularization (vein graft to right coronary artery) and aortic valve replacement 3 years previously. **(A)** CT volume-rendering image clearly demonstrates 2 areas of focal stenoses in proximal right **(black arrowhead)** and left **(large white arrow)** coronary arteries, a patent vein graft to the mid right coronary artery **(white arrowheads)**, and the metallic aortic valve ring **(small arrows). (B to D)** Conventional coronary angiography confirms both semiocclusive stenoses at the origin of right and left coronary arteries **(arrows in B and C)**. Also notice the slow filling of distal right coronary artery **(small arrows in B)** due to the decreased flow velocity. More than 90% of coronary lesions in TA are ostial or proximal, in accordance with the theory of a direct extension of aortic disease.

which is in agreement with previous reports (7) and may predispose patients to sudden death and/or potentially extensive myocardial infarction. Although there was no significant difference in Numano classification between patients with and without coronary artery involvement, there was a tendency toward more frequent disease of the ascending aorta in the former group. This might be because coronary involvement is due to a direct extension of aortic disease, and histological studies have demonstrated typical changes of inflammatory panarteritis (including the coronary arteries) involving the media and the adventitia (6).

All significant lesions were noncalcified, making traditional atherosclerosis unlikely as the main mechanism of disease. The initial involvement of the vessel wall is noted in the adventitia and ultimately causes fibrosis, calcification, and secondary stenotic lesions (30). There was a nonsignificant difference in age at the time of coronary CT angiography and the onset of symptoms between the group with coronary involvement and the nonlesion group. However, a significant difference in the duration of the disease existed between the coronary involvement group and the nonlesion group (176 vs. 21 months, $p = 0.01$). These findings suggest an increasing risk for coronary involvement as disease progresses (31).

To our knowledge, this is the first series of patients with TA with cardiovascular symptoms evaluated by coronary CT angiography. CT angiography could clearly demonstrate a different pattern of coronary involvement in our patients compared with conventional atherosclerotic coronary artery

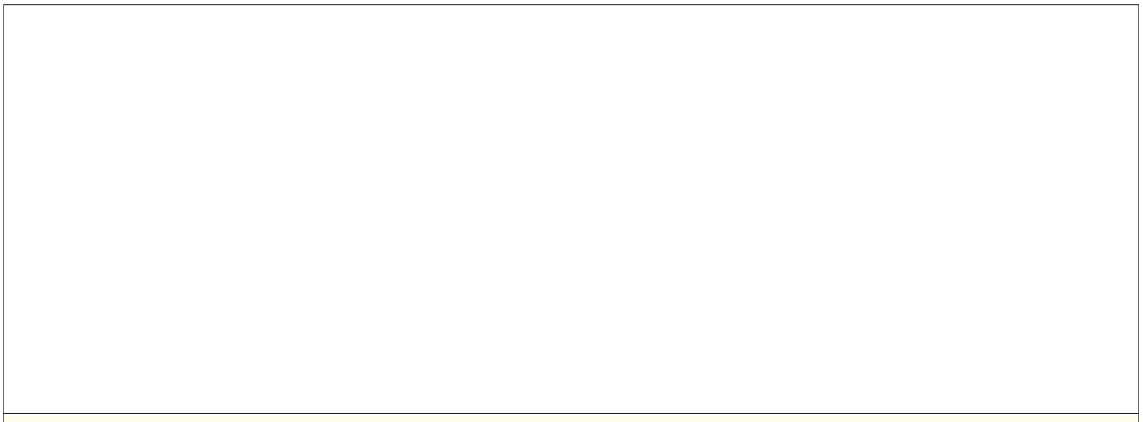

Figure 4. Nonstenotic Coronary Lesions in Takayasu Arteritis

(A) Multiplanar reconstructed image obtained by coronary computed tomographic (CT) angiographic image showing a completely calcified plaque at the origin of the left main coronary artery, without significant stenosis **(arrow)**, in a 58-year-old patient. **(B)** Multiplanar reconstructed coronary CT angiographic image showing noncalcified plaque, without significant stenosis, at the ostium of the right coronary artery **(arrow)** in a 26-year-old patient.

disease, and it is important to note that all significant lesions were noncalcified. As previously described, MDCT is a reliable tool for diagnosing and assessing aorto-ostial lesions (22). Once the diagnosis of coronary involvement is established, treatment should be multidisciplinary. Surgical and percutaneous revascularizations have proven successful (32). However, before revascularization, active disease should be excluded or treated, because adverse results have been observed in these patients when they are subjected to interventional or surgical treatment (6,33).

Study limitations. The small sample size precludes firm conclusions about the true prevalence of coronary involvement in TA and its association with the activity of the disease. Invasive coronary angiography was not performed in all patients to verify agreement between both methods. However, CT angiography has been demonstrated to be reliable, especially for detecting proximal coronary artery involvement (28). The prevalence of TA in the general population is low, so it is not mentioned in the appropriateness criteria for cardiac computed tomography (10). Nevertheless, given our results, it may be appropriate to use coronary CT angiography in these patients, especially if they have symptoms that may indicate coronary ischemia.

CONCLUSIONS

In this series of patients with TA and symptoms of angina or dyspnea, we found a high prevalence of coronary involvement despite their young average age, and most lesions were ostial or proximal in location. Coronary CT angiography is a noninvasive technique that can be used in patients with TA to assess the presence of coronary involvement, and it may be advisable to use it even in early stages of disease, especially if there is involvement of the ascending aorta.

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