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BRIEF COMMUNICATION

Structural Thickening of Medial Layer in Coronary Artery With Spasm in Patients With Myocardial Infarction

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BACKGROUND: The underlying pathophysiology of coronary artery spasm (CAS) remains unclear. We aim to determine whether coronary artery medial layer thickness is associated with CAS using optical coherence tomography.

METHODS AND RESULTS: A total of 50 patients with previous myocardial infarction underwent optical coherence tomography of the left anterior descending artery: 20 with CAS and 30 without CAS. Intimal and medial layer areas were measured by planimetric analysis of optical coherence tomography images. The medial area/external elastic membrane (EEM) area was significantly greater in patients with than without CAS (0.13±0.01 versus 0.09±0.01, respectively, $P<0.01$), whereas the intimal area/EEM area was similar in the 2 groups. In patients without CAS, the relationship of intimal area/EEM area with medial area/EEM area and coronary diameter response to intracoronary injection of acetylcholine was characterized by an inverted U-shaped curve ($y=-1.85x^2+0.81x+0.01$, $R^2=0.43$, $P<0.001$) and a U-shaped curve ($y=2993.2x^2-1359.6x+117.1$, $R^2=0.53$, $P<0.001$), respectively. Thus, the medial layer became thin and the contractile response became weak in coronary arteries with greater intimal area in the non-CAS patients. In contrast, in patients with CAS, the intimal area/EEM area had no significant relationship with the medial area/EEM area in either linear correlation analysis or quadratic regression analysis. Thus, even when the intimal layer thickened, the medial layer did not thin in patients with CAS.

CONCLUSIONS: The structural thickness of the coronary medial layer was increased in patients with CAS, which may provide mechanistic insight into the pathogenesis of CAS.

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Key Words: coronary atherosclerosis ■ coronary spasm ■ coronary vasomotion ■ optical coherence tomography ■ smooth muscle

The mechanisms underlying coronary artery spasm (CAS) remain unclear.[1] Atherosclerotic coronary arteries have impaired endothelium-dependent relaxation and enhanced reactivity of smooth muscle to acetylcholine, which synergistically cause a hyperconstrictive response to agonists.[2] Thus, it was reasonable to assume that CAS may be highly prevalent in coronary arteries with advanced atherosclerosis. However, a number of previous reports have demonstrated that CAS is more prevalent in angiographically normal or near-normal coronary arteries.[1,3] The reason for this discrepancy remains unclear. Recently, we showed that the medial layer was thinned in coronary arteries with advanced atherosclerosis in patients without CAS using optical coherence tomography (OCT),[4] which was consistent with prior findings based on histological analysis.[5,6] We found that thinning of the medial layer was related to the attenuated contractile response to acetylcholine in coronary arteries with the development of advanced atherosclerosis.[4] Therefore, we hypothesize that the thickness of the medial layer may have a significant impact on the contractile response to agonists in coronary arteries with spasm.

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The present study assesses whether CAS may be associated with a thickened medial layer in the coronary artery using OCT.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Patients and Study Protocol

We screened 74 consecutive patients who presented to Yamanashi University Hospital between January 2017 and May 2019 with a first acute myocardial infarction caused by occlusion of a proximal segment of the left anterior descending (LAD) artery and received successful reperfusion therapy by primary percutaneous coronary intervention. Patients with residual stenosis <50% in the LAD were included. Those with prior percutaneous coronary intervention to the LAD, history of coronary artery bypass surgery, cardiovascular events within 6 months after acute myocardial infarction, and congestive heart failure within 1 week of acute myocardial infarction were excluded. After applying these inclusion and exclusion criteria, 63 patients were examined for OCT and the provocation test for CAS. Written informed consent was obtained from all study patients before study. The study was approved by the ethics committee of Yamanashi University Hospital and conformed to the principles outlined in the 1975 Declaration of Helsinki.

This study was a subanalysis of the data from the observational study that was registered at URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000021340 (Unique identifier: UMIN000018432).

All patients underwent cardiac catheterization, including a coronary vasomotor function test and OCT, 6 months after acute myocardial infarction. Vasodilators including calcium channel blockers were withdrawn >3 days before the coronary vasomotor test.

Measurement of Epicardial Coronary Diameter Responses to Acetylcholine and Sodium Nitroprusside

Details of the procedure are previously described.[4] Briefly, incremental doses of acetylcholine chloride (OVISOT; Daiichi Sankyo, Tokyo) (5, 10, 50, and 100 μg/min) were infused into the left coronary artery.[4] Thereafter, intracoronary sodium nitroprusside (SNP) (10 μg/min) was infused in the same manner as acetylcholine. Quantitative coronary angiography (QCA) was performed in patients without CAS. The luminal diameter in a segment 20 to 35 mm from the distal edge of the stent in the LAD was measured quantitatively (QAngio XA; Medis Medical Imaging Systems, Leiden, The Netherlands). QCA analyses included the segment of the LAD where OCT analyses were performed. The greatest constrictor response among the responses to the 4 acetylcholine doses was selected as the coronary diameter response to acetylcholine for each patient without CAS.

Criteria for CAS Positive and Negative Tests

A CAS positive test was defined as transient total occlusion or near total occlusion (99% narrowing) with washout delay of contrast in the LAD. A negative CAS test was defined as <90% narrowing of LAD with neither anginal symptoms nor ischemic ECG changes in response to acetylcholine. This study also excluded patients with CAS in the left circumflex coronary artery but not LAD in response to acetylcholine.

OCT Image Acquisition and Analysis

Details of the procedure have been previously described.[4] Briefly, after measurement of epicardial coronary artery diameter response to acetylcholine and SNP, OCT in the LAD was performed using the Dragonfly JP intracoronary imaging catheter and the ILUMIEN OPTIS OCT imaging System (St. Jude Medical). All images were acquired after relaxation by intracoronary administration of 0.2 mg of nitroglycerin. OCT images were analyzed using a dedicated software program (Qlvus; Medis Medical Imaging Systems Inc., Leiden, The Netherlands) and ImageJ (National Institutes of Health, Bethesda, MD). Cross-sectional OCT images were obtained in the LAD along the coronary segment where CAS occurred or QCA was performed.[5] Three consecutive cross-sectional OCT images were analyzed in each patient over a 2-mm interval along a coronary segment distal to the distal stent edge in the LAD. All 3 cross-sectional OCT images assessed the medial layer, which was discernible along a continuous arc of >270° relative to the center of the lumen. The medial layer was seen as a dark band delimited by the internal elastic membrane and external elastic membrane (EEM) (Figure 1A). The lumen cross-sectional area (CSA), intimal layer area (internal elastic membrane CSA minus lumen CSA), and medial layer area (EEM CSA minus internal elastic membrane CSA) were measured by planimetric analysis on each of the 3 cross-sectional OCT images. The area of the intimal and medial layers was normalized by the EEM CSA on each OCT image. This study classified OCT-based tissue characteristics of the intimal area as follows: (1) fibrous tissue: homogeneous, signal-rich regions with low attenuation, (2) lipid: signal-poor regions without sharp borders, and (3) calcification: well-delineated,

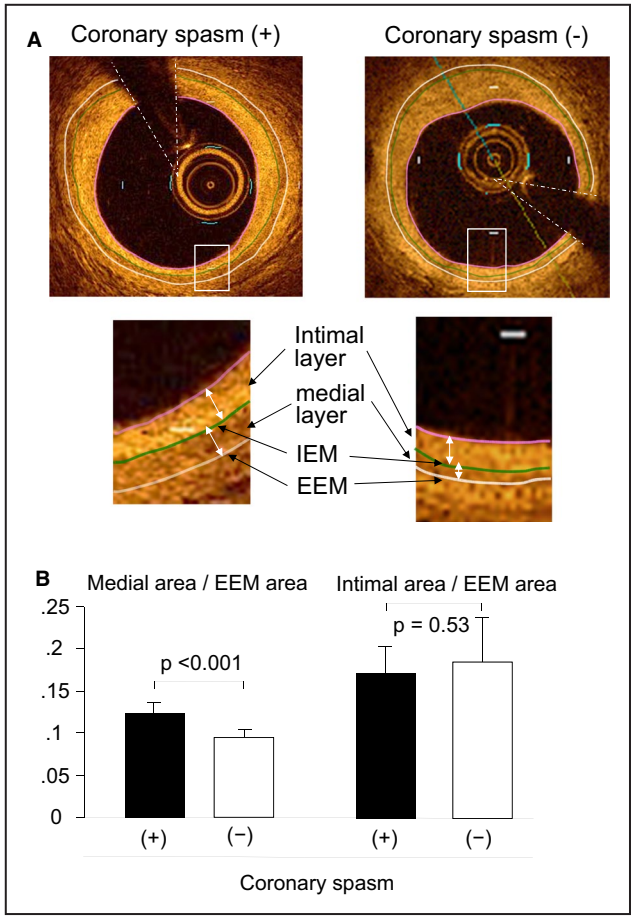

Figure 1. OCT images and comparison of each area of the LAD between patients with and without CAS.
A, Planimetric analysis of the OCT image and magnification of the rectangular areas in their images in coronary artery with spasm (left images) and without spasm (right images). The red line indicates lumen contour, the green line indicates the boundary of the IEM, and the white line indicates the boundary of the EEM. **B**, Comparison of medial area/EEM area and intimal area/EEM area between coronary arteries with (n=20) and without (n=30) spasm. CAS indicates coronary artery spasm; EEM, external elastic membrane; IEM, internal elastic membrane; LAD, left anterior descending artery; and OCT, optical coherence tomography.

signal-poor regions with sharp borders. The extent of each tissue was expressed as a sum of the arc angle with the respective OCT characteristics relative to the center of the lumen in each OCT image. The measurements on each OCT image were averaged over the 3 OCT images for an individual patient.

Statistical Analysis

Data were expressed as either the mean±SD, median and interquartile range (25th and 75th percentile), or frequencies (%), as appropriate. Normality of the continuous variables was assessed with Shapiro–Wilk test. Non-normally distributed data were expressed as the median and interquartile range (25th and 75th percentiles). Continuous variables between 2 groups were compared using Student paired or unpaired *t* tests or a Mann–Whitney *U* test, as appropriate. Categorical variables between 2 groups were compared using a χ^2 analysis or Fisher exact test. Linear and quadratic regression models were used to assess the relationship between 2 parameters. When both models had a statistically significant relationship, linear versus quadratic model fits were compared using the Bayesian Information Criterion. Statistical significance was defined as $P<0.05$. All analyses were assessed using STATA 13.0 (StataCorp, College Station, TX).

RESULTS

Comparison of Clinical Characteristics Between Patients With and Without CAS

CAS was induced in the LAD of 22 patients. Thirty-three patients had a CAS negative test. Among these patients, 2 patients with CAS and 3 patients without CAS were excluded from the study because of lack of suitable coronary artery segment for OCT or QCA analysis. The remaining 20 patients with CAS and 30 patients without CAS were included in the final analysis. Frequency of current smoking was significantly higher in patients with CAS compared with those without CAS (Table 1). The baseline diameter of the LAD before the coronary vasomotor function test using acetylcholine and SNP was significantly smaller in patients with CAS compared with those without CAS (Table 1). The dilator response of the LAD to SNP on QCA did not differ between the 2 groups (Table 1). The prevalence of high extent of lipid plaque and calcium deposition in the intima was not different between patients with and without CAS (Table 1).

Comparison of Extent of Coronary Medial Area Between Patients With and Without CAS

Intimal and medial layers were measured using OCT after complete relaxation of the coronary artery with intracoronary administration of nitroglycerin to avoid potential influence of spontaneous coronary artery constriction at baseline. The medial area/EEM area was significantly greater in patients with CAS compared with without CAS (Table, Figure 1B). The intimal area/EEM area was similar between patients with and without CAS (Table, Figure 1B).

Relationship Between Areas of the Intimal and Medial Layers in Patients With or Without CAS

In patients without CAS, the relationship between the intimal area/EEM area and medial area/EEM area was characterized by an inverted U-shaped

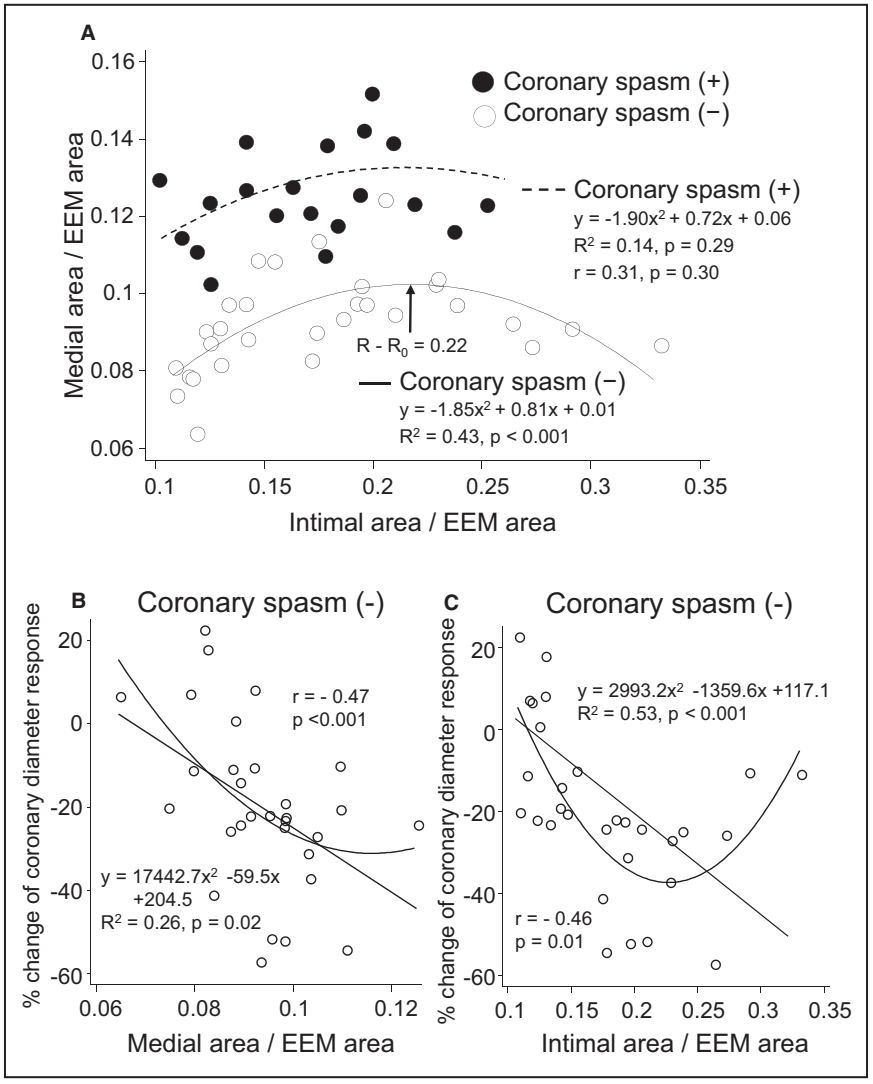

Figure 2. Relationship between intimal and medial area of the LAD and between each area and coronary diameter response to acetylcholine.
A, Relationship between the intimal area/EEM area (*x* axis) and the medial area/EEM area (*y* axis) in coronary artery with spasm (closed circles, n=20) and without spasm (open circles, n=30). The quadratic regression model shows a significant relationship between intimal/EEM area and medial area/EEM are in coronary artery without spasm (solid line). In contrast, no relationship with either the quadratic regression model or liner correlation model was observed in coronary artery with spasm (broken line). **B**, Relationship between the medial area/EEM area (*x* axis) and the percent change of coronary diameter response to acetylcholine (*y* axis) in patients without CAS. Percent (%) change of coronary diameter response is defined as (diameter after acetylcholine−diameter at baseline) x 100/diameter at baseline. The lower the % change of coronary diameter response, the stronger the contraction. Both linear and quadratic models had a significant relationship and they may fit equally on the basis of Bayesian Information Criterion score (264.2 vs 266.0, respectively). **C**, Relationship between the intimal area/EEM area (*x* axis) and the percent change of coronary diameter response to acetylcholine (*y* axis) in patients without CAS. The lower the % change of coronary diameter response, the stronger the contraction. Both linear and quadratic models had a significant relationship. The quadratic relationship was a better model than the linear relationship on the basis of Bayesian Information Criterion score (252.4 vs 264.6, respectively). CAS indicates coronary artery spasm; EEM, external elastic membrane; and LAD, left anterior descending artery.

curve, fitted to a quadratic regression model (y=−1.85x^2+0.81x+0.01, R^2=0.43, P<0.001, y axis; medial area/EEM area, x axis; intimal area/EEM area) (Figure 2A, open circles). This relationship had no significant linear correlation (r=0.30, P=0.10). Thus, the coronary artery medial layer became thinner with

Table. Clinical Characteristics of Study Patients

	All Patients (n=50)	Non-CAS (n=30)	CAS (n=20)	*P* Value
Age, y	66 (62, 73)	64 (60, 71)	69 (63, 76)	0.22
Male sex, n (%)	42 (84.0)	24 (80.0)	18 (90.0)	0.35
Current smoking, n (%)	16 (32.0)	6 (20.0)	10 (50.0)	0.03
Diabetes mellitus, n (%)	13 (26.0)	10 (33.3)	3 (15.0)	0.20
Hypertension, n (%)	35 (70.0)	22 (73.3)	13 (65.0)	0.53
Creatinine, mg/dL	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)	0.8 (0.8, 1.0)	0.75
HbA1c (%)	5.9 (5.6, 6.1)	6.1 (5.6, 6.5)	5.9 (5.6, 6.1)	0.14
LDL cholesterol, mg/dL	87 (77, 94)	87 (79, 93)	86 (74, 94)	0.94
HDL cholesterol, mg/dL	40 (35, 51)	40 (34, 53)	42 (38, 49)	0.94
Baseline diameter of the LAD, mm	2.2±0.34	2.3±0.28	2.1±0.39	<0.05
BMS, n (%)	12 (24.0)	6 (20.0)	6 (30.0)	0.42
Second-generation DES, n (%)	34 (68.0)	22 (73.3)	12 (60.0)	0.32
Third-generation DES, n (%)	4 (8.0)	2 (6.7)	2 (10.0)	1.0
Dilatory response to SNP (%)	16.9±10.2	18.1±10.5	15.1±9.7	0.32
Intima area/EEM	0.17±0.05	0.18±0.06	0.17±0.04	0.53
Medial area/EEM	0.11±0.01	0.09±0.01	0.13±0.01	<0.001
Arc angle of lipid tissue, n (%)				
0°–30°	9 (18.0)	5 (16.7)	4 (20.0)	1.0
30°–60°	14 (28.0)	9 (30.0)	5 (25.0)	0.76
>60°	2 (4.0)	2 (6.7)	0 (0.0)	0.51
Arc angle of calcification, n (%)				
0°–30°	6 (12.0)	4 (13.3)	2 (10.0)	1.0
>30°	2 (4.0)	2 (6.7)	0 (0.0)	0.51
β-Blockers	21 (42.0)	15 (50.0)	6 (30.0)	0.16
ACE-I/ARB	39 (78.0)	22 (73.3)	17 (85.0)	0.33
Calcium antagonists	43 (86.0)	23 (76.7)	20 (100.0)	0.02
Aspirin	50 (100)	30 (100)	20 (100)	…
Thienopyridines	49 (98.0)	30 (100)	19 (95.0)	0.22
Biguanide	4 (8.0)	3 (10.0)	1 (5.0)	0.64
DPP-4 inhibitors	6 (12.0)	5 (16.7)	1 (5.0)	0.38

Data are expressed as mean±SD, median (25th and 75th percentiles), or number (%) of patients. *P* value, comparison between patients with and without coronary spasm. Hypertension was defined as >140/90 mm Hg or use of antihypertensive medication; diabetes mellitus was defined according to the American Diabetes Association criteria or taking an antidiabetic medication. The extent of each tissue in the intimal area was expressed as a sum of the arc angle with the respective OCT characteristics relative to the center of the lumen in each OCT image. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare metal stent; CAS, coronary artery spasm; DES, drug-eluting stent; DPP-4, dipeptidyl peptidase; EEM, external elastic membrane; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; OCT, optical coherence tomography; and SNP, sodium nitroprusside.

greater atherosclerosis in patients without CAS. In contrast, in patients with CAS, there was no significant relationship between the medial area/EEM area and the intimal area/EEM area in either quadratic regression analysis or linear correlation analysis (Figure 2A, closed circles). Thus, even when the intimal layer thickened, the medial layer did not become thin in patients with CAS.

Relation of Coronary Diameter Response to Acetylcholine With the Extent of the Intimal and Medial Layer Areas in Patients With Non-CAS

The medial area/EEM area had a significant relation with coronary diameter response to acetylcholine in patients without CAS using both linear and quadratic models (r=−0.47, P<0.001, and R^2=0.26, P=0.02, respectively) (Figure 2B). The linear and quadratic models fitted equally on the basis of Bayesian Information Criterion score (264.2 versus 266.0, respectively). The intimal area/EEM area had a significant relation with coronary diameter response to acetylcholine in patients without CAS using both linear and quadratic models (r=−0.46, P=0.01, and R^2=0.53, P<0.001, respectively) (Figure 2C). The quadratic relationship was a better model than the linear relationship on the basis of Bayesian Information Criterion score (252.4 versus 264.6, respectively). Thus, the coronary contractile response to acetylcholine was not necessarily increased in coronary arteries with greater intimal area in patients without CAS.

Relation of Coronary Dilator Response to SNP to the Area of the Intimal and Medial Layers in Patients With CAS and Non-CAS

The coronary dilator response to SNP had no significant relationship with either the intimal area/EEM area or medial area/EEM area in linear correlation analysis or quadratic regression analysis in either patients with CAS and non-CAS (data not shown).

DISCUSSION

Our study reveals that the structural thickness of the coronary medial layer was increased in patients with CAS after relaxation of the coronary artery with nitroglycerin. A previous report showed that the medial layer in coronary artery with spasm was thicker at baseline before administration of nitroglycerin compared with those without spasm.[7] The thickened medial layer in coronary artery with spasm at baseline described in that report[7] reflected the transient rise of medial smooth muscle because of its spontaneous constriction, not the structural thickening of the medial layer itself seen after complete relaxation with nitroglycerin.

We have previously shown that coronary endothelial NO activity is reduced in patients with CAS.[8] Prior animal experiments show that NOS gene deficiency can result in arterial medial thickening because of an increase in proliferation of medial smooth muscle cells.[9] Thus, an impairment of endothelial NO activity may play a possible role in the medial thickening of coronary artery with spasm. However, it is unclear whether proliferative phenotype of the medial smooth muscle cells may affect spasmogenic activity in coronary artery with spasm. Additionally, apoptosis of medial smooth muscle cells is associated with medial thinning and weakened contractile response in the atherosclerotic artery.[10] Inflammatory infiltrates around lipid plaques participate in apoptosis of medial smooth muscle cells,[11] leading to medial thinning in the advanced atherosclerotic artery.[5] In patients with CAS, the intimal lesion of coronary artery at the spasm site was characterized with fibrous tissue, but had few lipid plaques.[12] Thus, it is possible that coronary artery with spasm may have fewer inflammatory changes, leading to reduction of medial smooth muscle cell apoptosis. This may subsequently prevent medial thinning in coronary arteries with spasm. The low burden of atheromatous and lipid changes in coronary artery with spasm may partly be explained by the relatively low prevalence of traditional atherosclerotic factors except smoking in patients with CAS.[13] During advanced stages of atherosclerosis, the medial layer of the coronary artery may become thinner and lose contractile force.[4–6] In this regard, when atherosclerosis highly develops, the coronary artery with spasm might lose spasmogenic activity. This could possibly explain the low frequency of CAS in patients with advanced coronary atherosclerosis.

The present study analyzed infarct-related coronary artery that may have endothelial vasomotor dysfunction caused by ischemia–reperfusion injury and the drug-eluting stent. This study was conducted 6 months after myocardial infarction, at which time the ischemia–reperfusion endothelial injury could be restored.[14] Furthermore, the study patients were treated with second- or third-generation stents that may have less suppressive effect on endothelial function.[15] It is unclear whether these factors may affect the present results.

In conclusion, our findings show that the structural thickness of the medial layer is increased in the infarct-related coronary artery with spasm, providing mechanistic insight into the pathogenesis of CAS.

ARTICLE INFORMATION

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Disclosures

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